University of Dundee

DOCTOR OF MEDICINE

The effects of right ventricular pacing in the heart failure population

Elder, Douglas

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Degree of Doctor of Medicine

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Contents

1. Acknowledgements

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I would also like to thank my friends and family, in particular my wife Helen and our beloved children for providing constant support and encouragement throughout.

2. Declaration

I hereby declare that the work contained in this thesis was carried out during my appointment as Clinical Research Fellow in the Division of Medicine and Therapeutics in the University of Dundee (Ninewells Hospital and Medical School).

I certify that I am the sole author of this thesis and that, unless otherwise stated, all references have been consulted by me.

None of the work within this thesis has been accepted previously for a higher degree.

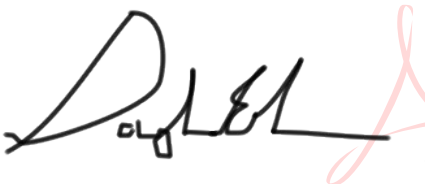
Dr. Henry Su managed the study visits and obtained the data from the “Right ventricular pacing impairs endothelial function in man” study, which was proposed and designed by Dr. Anna-Maria Choy. The analysis of the resultant data was performed by me and discussion as published and that contained within this thesis was written by me.

I conducted all the data preparation and analysis for the database studies, in particular I wrote the code to extract and interpret the echocardiographic data. I wrote the natural language processing algorhythm and undertook its validation through various iterations and prepared the data for linkage. I

filtered and prepared all the prescribing, hospitalisation, laboratory and outcome data and performed the record linkage using Stata software. I analysed the linked datasets and performed all the analysis personally with advice where needed from statistician colleagues.

I implanted the biventricular pacemakers for subjects in the *"Choosing the right pacing mode in heart failure"* study.

All the other studies in this thesis were conducted, analysed and reported by me unless otherwise stated.



Douglas Henry James Elder

5th August 2013

3. Summary of Contents

3.1 Description of work

Pacemaker implantation remains the sole treatment options for patients with bradycardia. The devices have evolved over the years, however recent studies of implantable defibrillators suggested that increased levels of pacing at the right ventricular apex (the conventional site) may be associated with worse outcomes in patients with impaired left ventricular systolic function.

An initial observational database linkage study was performed to investigate the prevalence of heart failure in patients referred for pacemaker insertion. This identified a significant portion of patients (19%) had heart failure and were potentially at risk. Further study was undertaken in patients without heart failure to investigate the effects of right ventricular (RV) apical pacing on endothelial function. 22 patients with sino-atrial node disease were exposed to high degrees of RV pacing and minimal RV pacing in a crossover study for 1 week each. This demonstrated significant impairment of endothelial function in the arm with a high degree of RV pacing.

A subsequent study investigated the impact of biventricular pacing compared to RV pacing again in a cross over design. Patients were implanted

with a biventricular device and randomised to RV only or biventricular pacing. Biventricular pacing was associated with significantly enhanced 6 minute hall walk distance together with improved quality of life and less impairment of endothelial function and reduction of hs-CRP when compared to biventricular pacing.

Finally a further retrospective data-linkage study demonstrated that angiotensin receptor blocker or angiotensin converting enzyme inhibitor use was associated with improved mortality and less hospitalisation for heart failure in patients paced for complete heart block, who were likely to be exposed to high degrees of right ventricular pacing.

In summary this thesis is a record of my study of the effects of pacemaker insertion in patients with impaired left ventricular systolic function. My research has demonstrated the potential detrimental effects of right ventricular apical pacing and has identified potential therapeutic strategies of ameliorating these effects.

3.2 List of abbreviations

6MWT	6-minute walk test
ACE	Angiotensin Converting Enzyme
AF	Atrial Fibrillation
ANOVA	Analysis of variance
ARB	Angiotensin Receptor Blocker
AV	Atrio-ventricular
BNP	B-type natriuretic peptide
BPM	Beats per minute
BVP	Bi-ventricular Pacemaker
CI	Confidence Interval
CRP	C-reactive protein
CRT	Cardiac Resynchronisation
CRT-P	Cardiac Resynchronisation Pacemaker
CRT-D	Cardiac Resynchronisation Defibrillator
CVA	Cerebrovascular accident
ECG	Electrocardiogram
EF	Ejection fraction
HF	Heart Failure
ICD	Implantable Cardioverter Defibrillator
ICD-9	International Classification of Diseases – revision 9
ICD-10	International Classification of Diseases – revision 10
IQR	Interquartile range

ISD	Information services division
LBBB	Left bundle branch block
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
LVSD	Left ventricular systolic dysfunction
MI	Myocardial infarction
NHS	National Health Service
NYHA	New York Heart Association
RH-PAT	Reactive Hyperaemia – Peripheral Arterial Tomography
RV	Right ventricular
SBP	Systolic blood pressure
SPSS	Statistical package for the social sciences
VT	Ventricular tachycardia
VF	Ventricular fibrillation

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Chapter 10 – Choosing the right pacing mode in heart failure

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3.4 List of Tables

Chapter 11 - The observed effects of Renin-Angiotensin System Blockers in patients paced for complete Atrio-Ventricular Block

4. Publications

4.1 Published Works

Pacing induced heart disease – understanding the pathophysiology and improving outcomes.

Elder DHJ, Lang CC, Choy A

Expert Rev Cardiovasc Ther. 2011 Jul;9(7):877-86.

Right ventricular pacing impairs endothelial function in man

Choy AM, Su H, Elder D, Noman A, Pauriah M, Struthers A, Lang CC

Europace. 2011 Jun;13(6):853-8

Renin-angiotensin system blockers are associated with reduced mortality and heart failure hospitalization in patients paced for complete atrioventricular block.

Elder DH, Lang CC, Rekhraj S, Szwejkowski B, George J, Pringle SD, Struthers AD, Choy AM.

Heart Rhythm. 2012 Apr;9(4):505-10. Epub 2011 Nov 1

5. Introduction

Since McWilliams et al(1)discovered the potential to stimulate myocardium with electricity in 1889; the development of the implantable pacemaker has developed significantly. It remains the definitive treatment for managing symptomatic bradycardia and hundreds of thousands of pacemakers are implanted worldwide each year(2). Whilst technology has continued to advance there has been an increased awareness of the potential detrimental effects of pacing in patients with heart failure. Trials designed to assess the benefits of dual chamber (atrio-ventricular) pacing versus single chamber (ventricular) backup pacing in heart failure patients with implantable cardioverter defibrillators (ICD) paradoxically demonstrated , previously unrecognised, adverse effects associated with long term right ventricular pacing in patients with structural heart disease(3).

The paradox is, of course, that many patients with sinus node disease and atrio-ventricular block tolerate right ventricular pacing well, and pacemaker implantation results in significant improvement in exercise capacity, and quality of life(4, 5). Indeed in patients with dilated cardiomyopathy, conventional dual chamber pacing has previously been shown to enhance cardiac output (6), this benefit was noted by optimisation of LV filling time facilitated by adjustment of the programmed AV delay.

Pacing from the right ventricular (RV) apex can induce dyssynchronous activation of the ventricles, analogous to that associated with intrinsic left bundle branch block.

Indeed, post hoc analyses of previous studies provide evidence to suggest that RV pacing *per se* may be associated with adverse cardiovascular effects; worse cardiovascular outcomes are associated with increased frequency of RV pacing (7-9) and the degree of ventricular dyssynchrony induced (10).

In parallel, as the benefits of biventricular pacing have been demonstrated in systolic heart failure with ventricular dyssynchrony associated with left bundle branch block (11, 12), the concept of 'pacing induced heart disease' caused by acquired dyssynchrony from right ventricular apical pacing, has gained recognition. Thus the avoidance of unnecessary RV apical pacing appears to be increasingly important (13).

5.1 Pacemakers and myocardial stimulation

Conventional pacemakers comprise a pulse generator which is usually positioned upon the pre-pectoral fascia below the left clavicle and pacing leads which travel from the pulse generator to the myocardium. Access to the endocardium is via the cephalic, sub-clavian or axillary venous systems leading the superior vena-cava and the right sided cardiac chambers. The pacemaker lead tip is either actively attached to the myocardium by a screw mechanism or plastic tines on passive leads become entangled in the trabeculum to hold the lead in position.

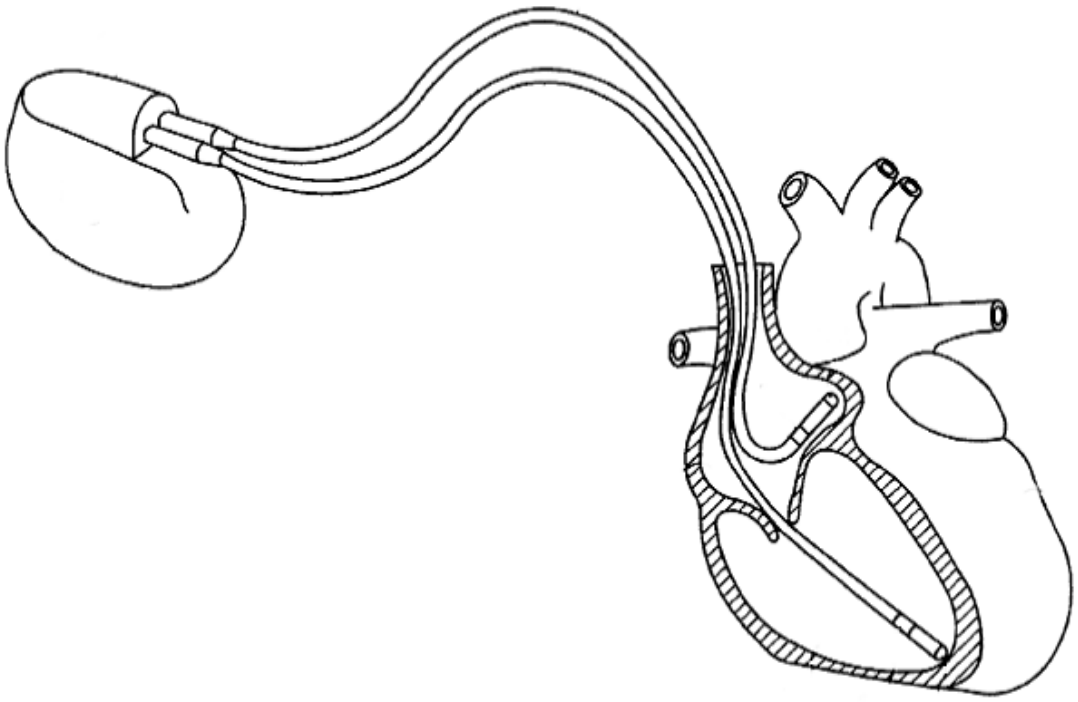


Figure 5.1 : Site of conventional pacemaker electrode placement

Image modified form original at www.freepatentsonline.com/6507756.pdf - Accessed 01/07/2011.

Once positioned an electrical impulse is delivered between two electrodes of the pacing lead. This potential difference between the electrodes creates a flow of electric current in the cardiac myocardium and the surrounding blood. If the electric current possesses certain characteristics, this will result in action potential creation, myocardial depolarisation and establish a self-propagating wave of electrical activity which spreads throughout the myocardium.

The electrical energy delivered to the myocardium from the pulse generator can be defined by its duration, waveform and amplitude (14, 15). Only impulses with a sufficient duration and amplitude will result in myocardial capture, the minimum energy delivered which results in myocardial capture is termed threshold.

The threshold for an individual is determined by many factors, including the size, shape and spacing of the electrodes on the pacing lead(16), the duration the pacing lead has remained in situ(17), the characteristics of the myocardium, e.g. pacing over scar(18), changes in sympathetic and parasympathetic tone(19) and the alignment of the pacing lead within the cardiac chamber.

The modern pacemaker is also able to sense intrinsic myocardial electrical activity and process this information. Pacemakers operate a series of timing cycles during which the pacemaker is able to sense electrical activity between the electrodes on the pacing lead. Dependent on the pacemaker mode, the pacemaker may, for example, only deliver a pacing impulse to the ventricle when an intrinsic impulse is not sensed within a specific time window.

5.2 Cardiac activation during sinus rhythm.

The heart's intrinsic conducting system is an efficient network of tissues with differing automaticity and conduction properties. The sino-atrial (SA) node sits high in the right atrium and under sympathetic and parasympathetic control determines the heart rate under normal circumstances. These specialised cells possess enhanced automaticity and depolarise at a rate of between 60 -100 bpm at rest. The action potential wave spreads across the atrium to the atrio-ventricular(AV) node. The AV node is the only means of electrical connection between the atria and ventricles. The AV node conducts the impulse at a much slower rate, taking approximately 80ms to conduct an impulse from the atrium to the ventricle. This in-built delay mechanism is important to facilitate completion of atrial depolarisation and contraction and allow time for adequate ventricular filling to occur. The conduction time through the AV node is again influenced by sympathetic activation.

Once the impulse passes through the AV node to the ventricle it is conducted through the specialised intraventricular conduction system. This is comprised of the His bundle and the purkinje fibres, the latter is initially sub-divided to the right, left anterior and left posterior bundles. These three purkinje tracts conduct electrical impulses at much higher rates that the surrounding myocardial tissue (3.5m/s v 0.6m/s)(20). The impulses are then "fanned out" through purkinje-myocardial junctions located in the antero-lateral RV wall and infero-lateral LV wall (21) this results in local myocardial

activation at these points, which in turn, creates a wave of activation which spreads through the myocardium. It should be noted that electrical activation of the right ventricle occurs approximately 10ms after the left (22) in the human heart.

The electrical activation of cardiac myocytes results in their contraction. The contraction is mediated by Ca++ influx into cells. This influx of calcium ions results in cellular contraction, however, there is a significant delay between the electrical activation of the cell, or depolarisation, and the peak force created by contraction – mechanical activation (23). This delay is approximately 30 ms. Thus peak cardiac contraction occurs approximately 30ms after the R wave on an electrocardiograph. This is termed electro-mechanical delay.

5.3 Cardiac activation during paced rhythm

Unlike sinus rhythm, a pacing stimulus from the RV apex causes myocardial activation almost in reverse direction to that which occurs in normal antegrade conduction using the His-Purkinje system. (Figure 5.2)

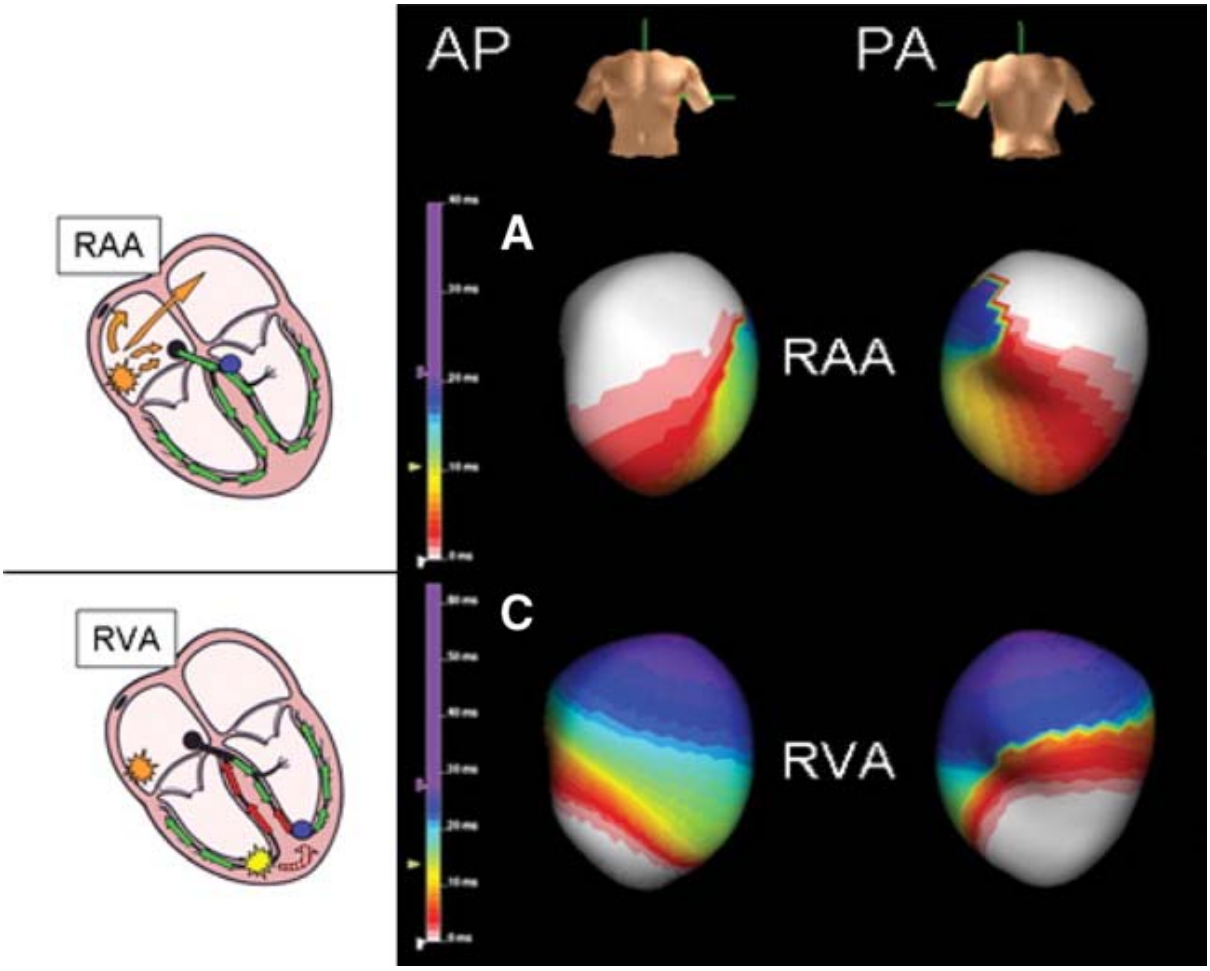


Figure 5.2 : Activation sequence of left ventricle resulting from a pacing impulse delivered in the right atrium and travelling over the his purkinje system (RAA) compared to a pacing impulse delivered in the right ventricular apex (RVA). The colourings depict time to activation with white showing areas of early activation and purple areas are activated late (~30ms after the white)

Image adapted from original: Single-site ventricular and biventricular pacing: investigation of latest depolarization strategy. Kimmel et al.

Both animal studies as well as clinical studies and have shown that pacing from the RV apex causes delayed and abnormal ventricular myocardial activation ('electrical' dyssynchrony) and dyssynchronous ventricular contraction ('mechanical' dyssynchrony)(24).

If we consider a model where a dual chamber pacemaker is in situ and there is no intrinsic activity, the pacemaker will deliver a pacing impulse to the atrium. This impulse will be delivered at the site of the atrial pacing lead e.g. the right atrial appendage and capture of the local myocardium will occur. The impulse will spread through the atrial myocardium and arrive at the AV node. If we assume that the AV node is non-functional and will not conduct the impulse to the ventricle, the pacemaker allow a pre-programmed time interval to elapse, e.g. 250 ms and subsequently deliver a pacing impulse to the ventricular electrode.

The ventricular impulse will result in local myocardial depolarisation at the site of the pacing lead, which is often at the right ventricular apex. This local depolarisation will then spread through the myocardium. In contrast to the intrinsic signals, conduction without using the purkinje fibres is significantly slower and leads to alterations in the sequence of myocardial activation(25). This occurs as the right ventricle is activated first, with conduction only reaching the left ventricle after some 50ms later than RV activation- so called inter-ventricular dyssynchrony. Furthermore on reaching the LV the spread of activation occurs slowly and heterogeneously , with the site of latest LV activation being the infero-posterior wall(22) this delay between the regional activation within the left ventricle(26) is termed intra-ventricular dyssynchrony.

The degree of dyssynchrony and activation sequence is determined by four mechanical properties(27) :

- Myocardial conduction is up to 4 times slower than his-purkinje conduction(28)

- Conduction occurs approximately 50% faster along muscle fibres, compared to perpendicular (29) to them resulting in the waveform spreading in an elliptical shape (30).

- Impulses generated within the myocardium itself rarely re-enter the his-purkinje system for propagation(21, 31). Furthermore recent studies have shown that such impulses can enter the purkinje system only at the truly apical aspect – the purkinje-myocardial junction. Given this site is often some way from the pacing site, significant time has elapsed prior to activation, and the impulse must travel from the distal purkinje fibre, to the proximal part of the his-purkinje system, prior to travelling distally to a remote site, the sequence of myocardial activation occurs mostly due to slow conduction through the normal myocardium(23, 32).

- Endocardial fibres conduct impulses faster than fibres in the rest of the LV. Thus a pacing impulse delivered endocardially will have a shorter time to electrical activation than if delivered from the epicardium.

This abnormal pattern of ventricular activation was originally thought to be akin to the abnormal activation patterns seen in left bundle branch block

(LBBB) (33), however recent studies have suggested the pattern of LV activation may differ in pacing induced LBBB compared to the intrinsic LBBB which occurs in systolic heart failure(34).

Thus pacing the ventricle from the RV apex leads to two distinct forms of dyssynchrony:

- *Electrical dyssynchrony* Electrical activation of the ventricle is from the RV apex as opposed to the purkinje system; this takes longer and is detectable on a 12 lead ECG as the QRS duration.

- *Mechanical dyssynchrony* Pattern of myocardial contraction occurs in an abnormal fashion as a result of electrical dyssynchrony, this is detectable by cardiac imaging.

Electrical and mechanical dyssynchrony both result in prolongation of the systolic phase of the cardiac cycle and a shortened diastolic phase thus compromising cardiac output by reducing diastolic ventricular filling and leading to functional mitral regurgitation. Shortened diastolic coronary

artery perfusion can also lead to relative myocardial ischemia and further impairment of systolic function. The presence of mechanical dyssynchrony has been associated with deterioration in overall LV systolic function(26).

5.4 Evidence for adverse cardiovascular outcomes associated with RV pacing from trials of pacing mode in patients with bradycardia.

There is no clear data on the impact of RV pacing in absolute isolation; rather it is inferred from carefully designed clinical studies. To pace the myocardium requires either a shortening of the atrio-ventricular delay to "beat" the AV node, to a sufficient extent to avoid fusion or pseudo-fusion, or an increase in the baseline pacing rate. There is clear data to suggest that altering the AV delay can have significant impact on cardiac output (35), and similarly, comparing markers of myocardial function at different heart rates also poses limitations.

The main focus of research into pacemakers and their function in patients with brady-arrhythmias has been to investigate whether dual chamber atrio-ventricular sequential demand pacing (DDD) offers benefits over either atrial demand pacing alone (AAI) for sinus node disease, or ventricular demand pacing alone (VVI) in either sinus node disease, or atrio-ventricular node disease. It might be expected that given atrio-ventricular sequential pacing is most akin to the sequence of chamber activation in sinus rhythm

and most approximates normal physiology, it would be superior to ventricular based pacing, however, this has never been conclusively demonstrated in randomised trials of pacing mode (13).

Furthermore, pacemaker trials have not demonstrated superiority of a particular pacing mode in terms of survival or heart failure, with the exception of a reduction in atrial fibrillation, and a modest reduction in stroke.

The Canadian Trial of Physiological Pacing (CTOPP) (36) compared physiologic atrial based pacing to ventricular only pacing in 2568 patients with sinus or atrio-ventricular node disease, and showed no significant reduction in the incidence of mortality or stroke, but a relative reduction in the incidence of chronic atrial fibrillation which reached 20.1% (95% percent confidence interval (CI), 5.4 to 32.5; *P*=0.009) after 6 years of follow-up (37). Similarly, the MOde Selection Trial (MOST) (38) that examined 2010 subjects with sinus node disease randomised to rate responsive ventricular based pacing (VVIR) or rate responsive dual chamber pacing (DDDR) pacing, reported a lower incidence of atrial fibrillation (hazard ratio (HR), 0.79; 95%,CI 0.66 to 0.94; P=0.008),and heart failure hospitalisation in the DDDR group compared to VVIR group. More recently, a detailed meta-analysis by Healey *et al* (13) of eight pacemaker trials comparing these two pacing modes and covering over 35,000 patient-years of follow-up found that atrio-ventricular pacing reduced atrial fibrillation (HR, 0.80; 95% CI, 0.72 to 0.89; *P*=0.00003), with a modest reduction of stroke but the magnitude of

these benefits did not translate to a reduction in mortality or reduction in heart failure.

In contrast the, albeit smaller, Danish study (39) of 225 patients with sick sinus syndrome over 5 years follow-up found beneficial effects on atrial fibrillation, thromboembolic events, heart failure and cardiovascular mortality with single chamber atrial pacing (AAI) when compared to VVI pacing. A further study by the same investigators compared AAIR with DDDR with short (increased RV pacing) or long AV (reduced RV pacing) delays in 177 patients over a mean follow up of nearly 3 years. There was again a lower incidence of atrial fibrillation in the AAIR group (7.3%) ($p = 0.03$) compared to the group pacing the ventricle (23.3% for short AV delay and 17.5 % for long) (40). The increased risk of atrial fibrillation observed in the RV pacing group may, however, be due to early truncation of atrial filling, which may result in a significant increase in atrial size, together with a decrease in left ventricular (LV) fractional shortening seen in the dual chamber groups.

The frequency of pacing in the RV appears to be directly correlated to adverse outcomes; although the critical level and duration at which RV pacing is deleterious remains unanswered. In the MOST study (7) the risk of heart failure hospitalisation and atrial fibrillation directly correlated with RV pacing burden, independent of pacing mode, with greatest risk seen in patients who had greater cumulative pacing in the ventricle.

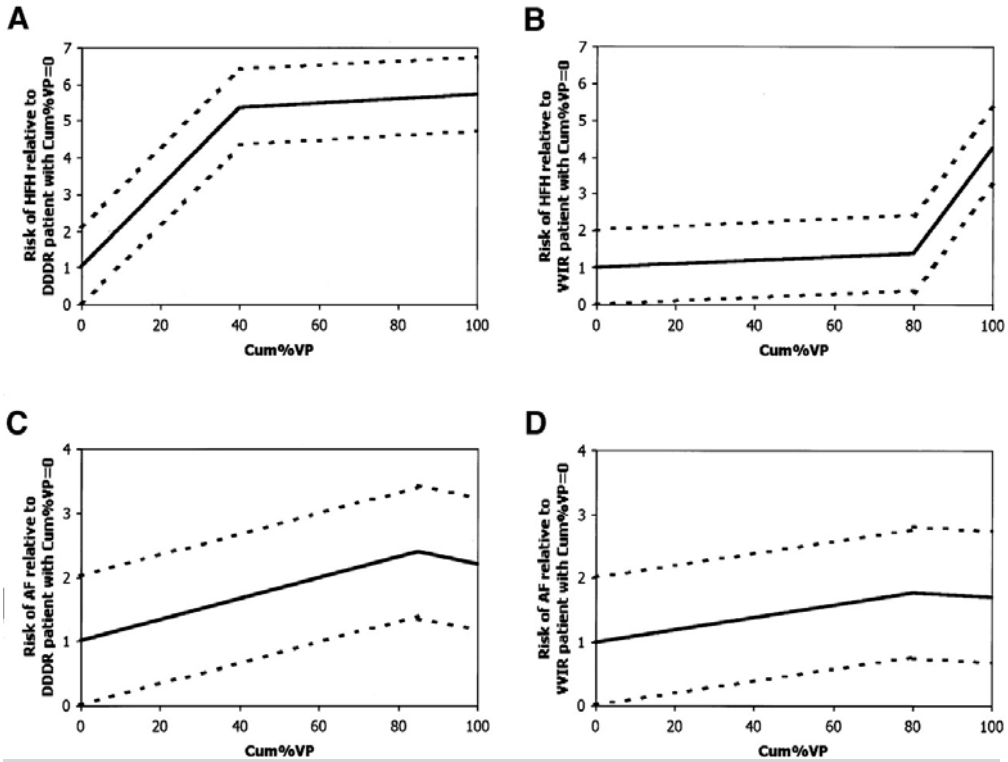


Figure 5.3 – Relationship between percentage pacing and outcome .

Relation of event risk to cumulative percent ventricular paced (Cum%VP) as estimated by Cox models with linear spline functions. Dashed lines represent 95% confidence intervals for point-by-point estimates of the hazard ratio for a 1% change in Cum%VP. A, DDDR mode, HFH; b, VVIR mode, HFH; c, DDDR mode, AF; d, VVIR mode, AF. Taken from : *Sweeney MO, Hellkamp AS, Ellenbogen KA et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 107(23), 2932-2937 (2003).*

The HR for HF hospitalisation in the DDD group was 2.99 [95% CI, 1.15 to 7.75] (for Cum%VP >40%) and in the VVIR group the HR was 2.56 [95% CI, 1.48 to 4.43] (for Cum%VP >80%). The relationship between atrial fibrillation and the percentage of pacing in the ventricle was demonstrated to be linear with DDDR, HR for AF 1.36 [95% CI, 1.09, 1.69] for each 25% rise in percentage V pace and ; HR 1.21 [95% CI 1.02, 1.43], for each 25% increase in cumulative percentage ventricular pacing in the VVIR group.

Table 5.1 summarizes the key findings of the major trials of pacing mode.

Table5.1 – A summary of the major trials of pacing mode and their outcome.

Trial	Date	Subjects	Follow -up (yrs)	Pacing mode	Conduction disturbance	Endpoint	Result
DANISH Study	1994	225	5.5	AAI v DDD	SND	Stroke , atrial fibrillation and death	Significant reduction in stroke, atrial fibrillation in and death AAI group.
PASE	1998	407	2.5	DDD v VVI	SND & AVB	Quality of Life	No difference in QOL Trend to less atrial fibrillation in SND
CTOPP	2000	2568	6.0	AAI / DDD v VVI	SND & AVB	Stroke or cardiovascular mortality Atrial fibrillation	No significant reduction in stroke or cardiovascular mortality. Significant reduction in atrial fibrillation with AAI/DDD
MOST	2002	2010	4.5	AAI v DDD	SND	All-cause mortality, Stroke Atrial fibrillation	No significant difference in all-cause mortality or stroke. Significant reduction in atrial fibrillation in DDD group
UKPACE	2005	2021	4.6	VVI v DDD	AVB	Stroke, Atrial fibrillation, Heart failure	No significant difference between any end-point for any group
DANPACE	2011	1415	5.4	AAI v DDD	SND	All-cause mortality Atrial Fibrillation	No significant difference in all-cause mortality. More atrial fibrillation in AAI mode
SAVE PACe	2008	1065	1.7	DDD -MVP*	SND	Atrial Fibrillation	Moderate reduction in atrial fibrillation with MVP

5.5 Evidence for adverse cardiovascular outcomes associated with RV pacing from implantable cardioverter defibrillator trials.

Studies in individuals with implantable defibrillators provided a unique opportunity to study the effects of pacing in patients who do not have a specific bradycardia indication, rather are at risk of sudden cardiac death, most often due to structural heart disease and poor left ventricular function.

This is possible given modern implantable cardioverter defibrillators have the ability not only to sense electrical activity and deliver defibrillation energy, but also to perform standard pacing functions. Furthermore, conventionally the defibrillator lead is placed in the right ventricle at the apex, to provide the optimal shock vector for the defibrillator.

The DAVID trial(3) studied 506 heart failure patients implanted with ICDs, but without bradycardia, and randomised individuals to dual-chamber sequential pacing at 70 b.p.m. or ventricular demand backup pacing at 40 b.p.m.

The former group, obviously, paced in the ventricle a significantly higher percentage of the time. In the analysis the authors report increased frequency of RV pacing (defined as > 40% of the time) was found to be associated with higher mortality and heart failure hospitalisation(9) in this cohort of heart failure patients. (Figure 5.4)

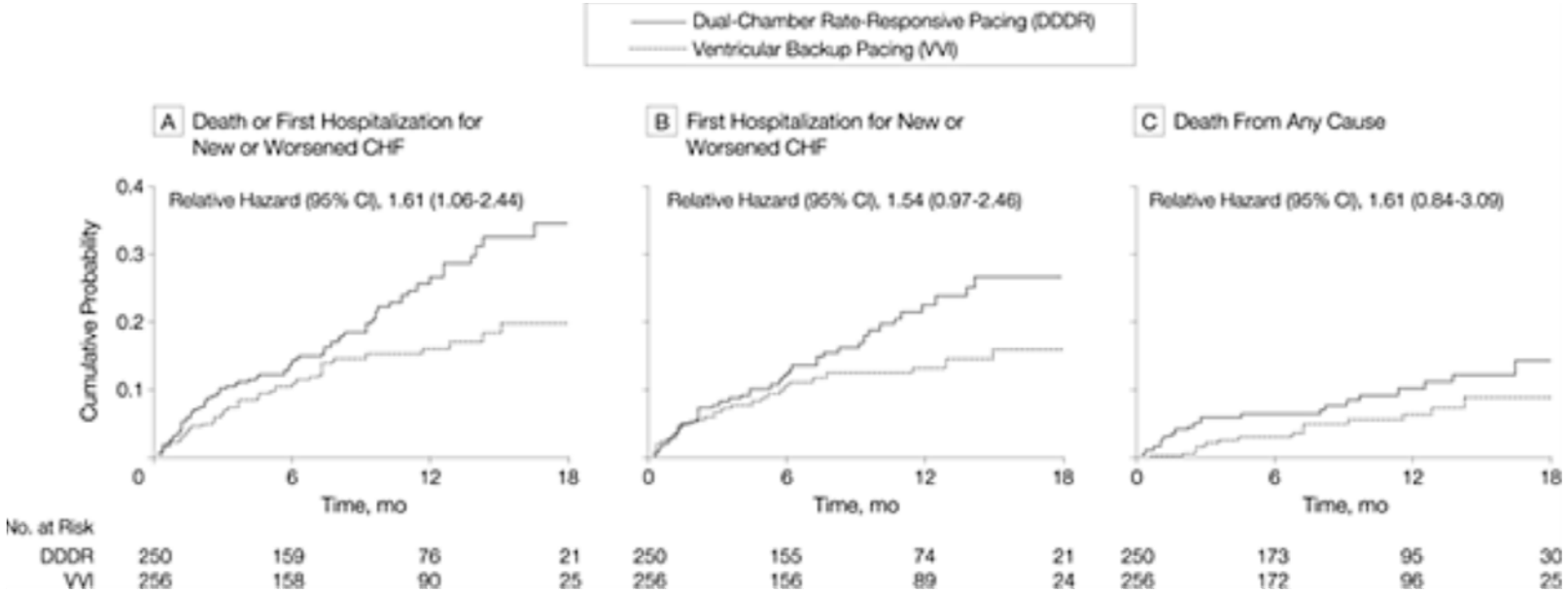


Figure5.4 - Survival to main end-points in the DAVID study by pacing mode.

Reproduced from : Wilkoff BL, Cook JR, Epstein AE et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. JAMA 288(24), 3115-3123 (2002).

5.6 Avoidance of unnecessary ventricular pacing.

Combining the results of these pacemaker and ICD trials, the inability to demonstrate clear clinical benefit of physiologic atrio-ventricular sequential pacing compared to ventricular demand pacing may be due to the increased RV pacing that occurs in atrio-ventricular pacing with short programmed AV delays. The evidence suggests that RV pacing *per se*, may be detrimental in terms of survival and heart failure, and may offset the benefits of preserving atrio-ventricular synchrony. If this were the case, then avoidance of unnecessary RV pacing should translate to better outcomes.

The SAVE PACe (41) study evaluated a novel pacing algorithm that sought to minimise ventricular pacing in 1065 patients with sinus node disease. The algorhythm itself permitted single non-conducted atrial events, and provided single back-up paced beats as required. If persistent AV block developed, the device “switched” to function in the DDD mode. Once switched the device periodically assessed for AV conduction and, if present assumes atrial based pacing once more. (Figure 5.5).

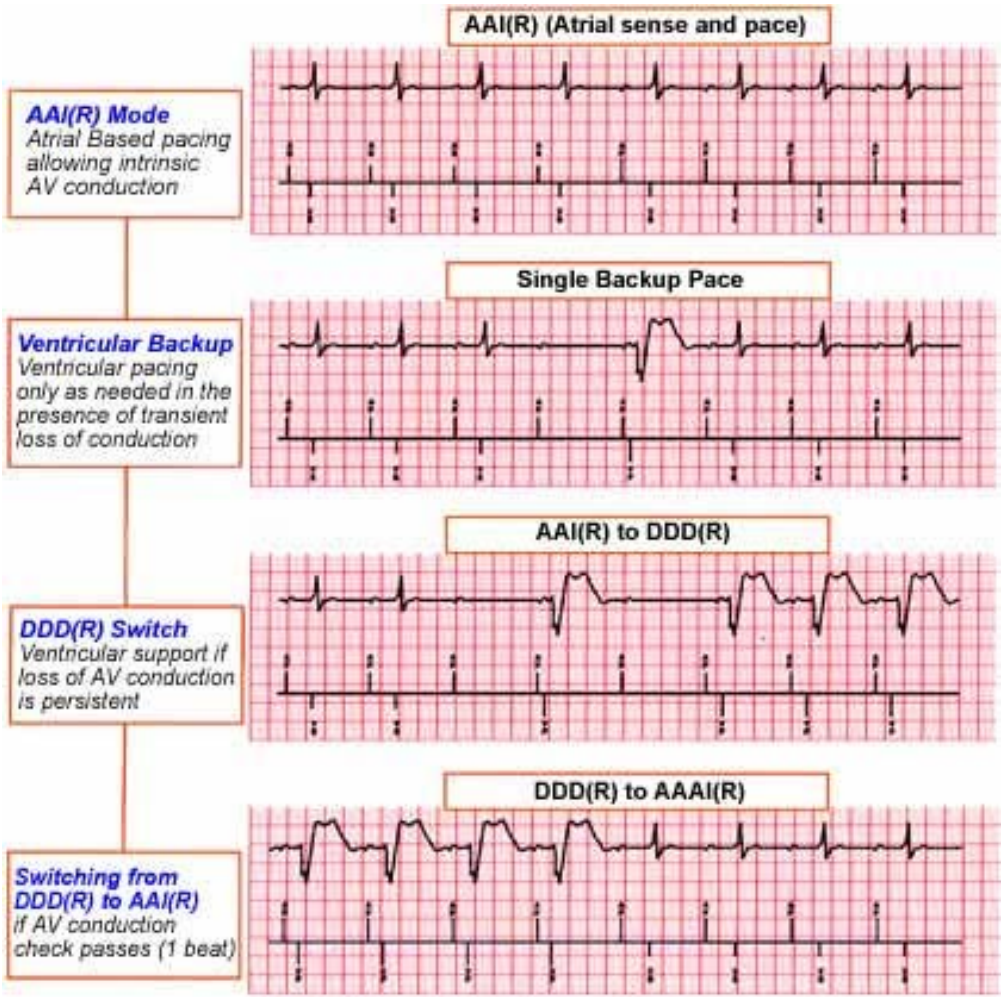


Figure 5.5 – Algorhythm used in the SAVE PACe study.

Sweeney et al ; Minimizing ventricular pacing to reduce atrial fibrillation in sinus-node disease, N Engl J Med, 357, 10 , 1000-8

The study reported a 40% early reduction in persistent atrial fibrillation in those randomised to dual chamber minimal ventricular pacing compared to those with conventional dual chamber pacing.

In contrast, the recently reported DANPACE (42) study of 1,415 patients with sick sinus syndrome randomised to single-lead atrial pacing or dual-chamber pacing found no difference in mortality, incidence of chronic AF, stroke and HF

between groups over a mean follow up of nearly five and a half years. In addition, paroxysmal atrial fibrillation occurred more frequently in the AAIR group. These results were unexpected and contradict the SAVE PACe and previous Danish study by Andersen et al. One possible explanation was that in the DANPACE study, algorithms were used to promote intrinsic conduction whereby programmed AV interval in the DDDR group was allowed to be slightly longer than previous trials (140-220 ms) and in individuals with no intrinsic conduction with an AV interval of greater than 220ms, the atrio-ventricular hysteresis function was enabled. This minimised the degree of *unnecessary* ventricular pacing and thus the percentage pacing in the DDDR group was only 65 ± 33%, which is lower than in the DDD group in the SAVE-PACE trial (99 %). This may partly explain the lack of deleterious effects usually observed with ventricular pacing. It is also likely that the deleterious effects of RV pacing may have greater impact in patients with structural heart disease or conduction disease (43) where the underlying disease substrate may contribute to the pathophysiological process(44) of impaired ventricular function, or cause a reduced cardiac capacity to accommodate the reduction in ventricular function caused by pacing induced dyssynchrony. More studies are required to define the populations at greatest risk of the detrimental effects of right ventricular pacing.

5.7 Adverse effects of right ventricular pacing

5.7.1 Adverse hemodynamic consequences of pacing induced electrical and mechanical dyssynchrony

Electrical and mechanical dyssynchrony may result in worsened haemodynamics primarily due to a decrease in cardiac output and impaired LV filling (45, 46). Nahlawi *et al* studied twelve patients with permanent pacemakers with ventricular leads at the right ventricular apex and intact AV nodal conduction, normal left ventricular function and no evidence of cardiac ischemia. The study demonstrated a significant acute reduction in ejection fraction (67% to 60% ($p<0.0002$), assessed by labelled blood pool imaging, after 2 hours of right ventricular apical pacing. Furthermore after 1 week of ventricular pacing the EF fell from (67 to 53 %, $p<0.0008$). (46). It should be noted that the AV delay in this study was programmed to 100ms to ensure a high percentage of RV pacing, however it could be argued that this led to truncation of RV filling. On cessation of pacing after 1 week, there was not, as might be expected, a return to the pre-pacing levels of EF. The EF remain suppressed during intrinsic ventricular activation (57%) albeit, improved compared to that during RV pacing (53%), $p<0.05$. Furthermore even a small reduction in EF has been associated with worse long-term outcome in the Framingham study(47).

Lieberman and colleagues studied a population of patients undergoing

electrophysiological study and considered the impact of pacing in different sites (RV apex, RV septum, RV free wall, LV free wall and simultaneous biventricular pacing) on acute measures of left ventricular function in patients with and without left ventricular systolic dysfunction{Lieberman, 2006 #4236}. When comparing each site to the baseline (AAI pacing at 10 b.p.m. greater than the sinus rate) the authors reported a fall in EF associated with all pacing sites in patients with LV EF > 40%, with the smallest reduction being in the biventricular group and the largest in the RV apex group. When considering patients with LVEF<40% biventricular pacing improved LVEF compared to baseline whereas RV apex was, again, associated with worsened EF in this population. Additionally acute RV pacing caused potentially deleterious reductions in cardiac output and stroke volume with impaired diastolic relaxation and increased LV end-diastolic pressure in patients with and without impaired LV function (48). These results were similar to those by Hay et al (49) who studied 9 patients with heart failure, and compared LV, RV and biventricular pacing. Biventricular pacing also improved systolic LV function, as did LV pacing alone only RV pacing was detrimental.

Current evidence suggests QRS width has only a limited relationship with dyssynchrony (50-53). Electrical dyssynchrony may result in a series of detrimental effects on cardiac function (24, 54, 55) but a widely accepted explanation for the increased incidence of heart failure in patients with RV apical pacing is mechanical dyssynchrony

5.7.2 Structural alterations

Chronic electrical and mechanical dyssynchrony can lead to structural changes over time. Studies have demonstrated adverse LV remodelling (56, 57), and mitral valve incompetence(58) as a result of RV pacing. In the aforementioned study by Nahlawi *et al*, chronic RV pacing after one week resulted in lower LV ejection fraction compared to the reduction observed with acute pacing(46). Significantly, the LV ejection fraction remained suppressed after discontinuation of RV pacing, suggesting structural changes within the myocardium.

Thambo *et al* examined 23 adult patients with complete congenital atrio-ventricular block who had ≥5 years of RV apical dual-chamber pacing and found that the associated ventricular dyssynchrony was associated with adverse LV remodelling, dilatation, asymmetrical hypertrophy, and overall lower exercise capacity than controls (59).

A study of RV biopsy specimens in patients paced for congenital AV block demonstrated significant myofibre size variation, fibrosis, fat deposition, sclerosis, and mitochondrial morphological changes(60). However it should be noted that some of these changes seen in the above two studies may be due to the underlying myocardial disease process in patients with complete heart block who are antibody positive(44) rather than as a direct result of the pacemaker.

Van Oosterhout(56) and colleagues demonstrated changes in myocardial mass and structure in a canine pacing model. Myocardium close to the pacing site became significantly thinner, whilst late activated regions became hypertrophied. Additionally cardio-myocyte diameter was significantly greater at sites remote to the pacing stimulus. The authors noted no alteration in overall pump function associated with pacing.

Vernooy et al(57) studied the impact of right ventricular pacing in patients after his-bundle ablation for atrial arrhythmias. They observed echocardiographic measures of cardiac size and function including LV diameter, weight, and ejection fraction together with atrial size and degree of mitral regurgitation. Individuals with normal left ventricular size and performance prior to ablation and RV pacing were noted to have increased left ventricular mass and size, together with higher degree of mitral regurgitation and decreased left ventricular ejection fraction at follow-up.

5.7.3 *Myocardial Strain*

The law of Laplace is a principle of physics that states that the tension on the wall of a sphere is the product of the pressure times the radius of the chamber and the tension is inversely related to the thickness of the wall. The term strain as used to describe the interaction between forces experienced by the myocardium was defined by Mirsky et al (61) as “A dimensionless quantity that represented the percent change in dimension from a resting state to one

achieved following application of a force (stress).” “Therefore, strain is the relative deformation of tissue from an applied force.”(62) Thus strain is an expression of the lengthening or shortening of fibres. Strain rate is the term given to the rate at which the changes in fibre length occur(62). When considered together, strain and strain rate, provide an overall measure of cardiac contractility and allow the observer to examine differences in contractility within regions of the myocardium.

Re-distribution of myocardial strain to different regions within the heart caused by heterogeneity in myocardial fibre contraction associated with right ventricular pacing (63-65) has been previously demonstrated by echocardiography. The myocardium at the RV apical pacing site contracts early and stretches not-yet-activated regions of the LV and further delays activation of the stretched region. Once late activation of the stretched region occurs, load is transferred to the earlier activated territories which undergo paradoxical stretch resulting in inefficient contraction (66, 67). Prinzen et al (68) studied patterns of myocardial strain by magnetic resonance imaging and reported significant heterogeneity of myocardial fibre contraction in the paced heart. There was virtually no myocyte fibre shortening at the pacing site, and up to a two-fold increase in workload at the site of latest activation usually the LV lateral wall (68) in RV apical pacing. Furthermore there were significant more regions with reduced work during RV apical pacing than during pacing at the base of the left ventricle. RV apical pacing was also observed to reduce global LV pump function in this study.

5.7.4 Impaired myocardial perfusion

Patients with left bundle branch block have been shown to have myocardial perfusion defects even in the absence of coronary artery disease (69, 70). Taking the hypothesis that the ventricular activation sequence with left bundle branch block, approximates that of right ventricular pacing, Tse et al studied 43 patients with right ventricular pacemakers implanted for complete heart block with radio nucleotide thallium-201 myocardial scintigraphy to assess myocardial perfusion and radionucleotide ventriculography to assess left ventricular function. They reported that patients with myocardial perfusion defects were likely to have been paced for longer. Furthermore those with perfusion defects subsequently underwent coronary angiography which revealed normal coronary arteries in 81 %, inferring that long term right ventricular pacing may result in abnormalities in myocardial perfusion.

Skalidis et al(71) subsequently undertook a similar study evaluating the coronary blood flow and reserve in patients with permanent pacemakers and normal coronary arteries at angiography. Coronary flow rates were noted to be significantly lower in patients with pacemakers compared to those without. Furthermore coronary flow reserve was also noted to be suppressed; suggesting abnormalities lay within the microvasculature. A further study by Ono et al (72) confirmed these previous findings and additionally reported alterations in glucose uptake in the septum, likely due to impaired systolic thickening and excess intramyocardial pressure at that site. Thus activation of the ventricular myocardium from the RV apex is associated with deficiencies in

myocardial perfusion (71, 73) and glucose uptake (72, 74) and this may occur as the result of the aforementioned redistribution of regional myocardial workload that occurs with right ventricular apical pacing (32, 68).

5.7.5 Diastolic dysfunction

Optimal LV filling is clearly important in determination of cardiac output and there have been a few studies exploring the effects of RV pacing on diastolic function, in an acute study, RV pacing caused impaired diastolic relaxation and increased LV end-diastolic pressure in patients with and without impaired left ventricular function (48). Hay and colleagues(49) demonstrated an improvement in diastolic function, as assessed by iso-volumetric relaxation time on pressure-volume loops, in acute biventricular pacing in 9 patients with heart failure. Other studies have centred on the relationship between diastolic indices and the atrio-ventricular (AV) interval in seeking to determine the optimum paced AV interval. Styliadis *et al* reported improvements in trans-mitral E/A wave ratio and augmentation of LV filling time with AV intervals decreasing from 200 ms to 100 ms in patients with DDD pacemakers for complete heart block. Additionally, levels of atrial natriuretic peptide progressively decreased with decreasing AV intervals. Optimal AV intervals (100 ms – 150 ms) were associated with improved diastolic indices and lower natriuretic peptides levels (75) suggesting that ventricular function in patients with a high degree of RV pacing is closely related to timing of atrio-ventricular delay. This is already recognized to be an important adjustable factor for patients who do not respond initially to biventricular pacing for heart failure.

5.7.6 Impaired Endothelial Function

Chronic right ventricular pacing has been shown to be associated with increased sympathetic activation (76, 77) as well as increased oxidative stress which is associated with reduced nitric oxide production (78). These indirect mechanisms can reduce endothelial function and are likely to have a role in the pathological effects of chronic right ventricular pacing. The impact of pacing on endothelial function has been investigated in the setting of biventricular pacing in patients with heart failure. Rubaj *et al* (78) demonstrated that biventricular pacing, which minimises ventricular dyssynchrony, reduced oxidative stress, NO metabolites and immune activation, and improved tissue perfusion, compared to right ventricular pacing in heart failure patients. More recently, Akar *et al* (79) reported that in patients with heart failure and electrical dyssynchrony as evidenced by QRS duration greater than 120ms, a positive response to cardiac resynchronization therapy (CRT) was more likely in patients with endothelial dysfunction before CRT. This same group have also reported that CRT improves endothelial function in patients with heart failure (80). It remains unclear whether patients receiving pacemakers for standard bradycardia indications, may be subject to endothelial dysfunction as a direct result of right ventricular pacing. Furthermore it is unclear whether the potentially detrimental effects on endothelial function in patients with right ventricular pacemakers may be ameliorated by biventricular pacing.

5.8 Strategies to avoid pacing induced cardiovascular disease

Although current pacemakers all provide algorithms to avoid unnecessary RV pacing, 40% of pacemaker patients have AV node disease and require chronic ventricular pacing(81) with 30% noted to have impaired left ventricular function(82). It remains unclear the percentage of patients who have pre-existing left ventricular dysfunction who are referred for a standard pacemaker, and therefore are at greatest potential risk of developing pacing induced heart disease. This is particularly important in young people with long term pacing requirements. Strategies to avoid pacing induced cardiovascular disease in patients with AV node disease have focused primarily on alternative pacing sites to minimise the electrical and mechanical dyssynchrony seen with RV apical pacing, and more recently on biventricular pacing. However, many questions still remain as to the selection of the optimal pacing mode and site, the selection of patients who would benefit, and whether pharmacologic therapies that modulated neuro-hormonal activation such as renin angiotensin aldosterone system blockers or beta-blockers may be beneficial.

5.8.1 Pacing In Sinus Node Disease

There remains reluctance in physicians to employ single lead atrial pacemakers in patients with isolated sinus node disease, due to concerns of AV node disease developing at a later stage. Although this risk has been shown to be low (0.6% annual risk) (39), nevertheless the risk of re-do procedures (to site a ventricular lead and upgrade to a dual chamber system) in patients with single lead atrial pacemakers is relatively high (22%), compared to ventricular

devices (12%)(42). In patients with intact AV node conduction, dual chamber pacemaker programming (83) to extend the AV delay beyond the intrinsic AV interval can effectively reduce the amount of pacing in the ventricle (41, 75). Many modern pacemakers can perform this automatically using algorithms to promote intrinsic conduction but with the ability to pace the ventricle (84, 85) should AV block occur , as previously discussed, and this strategy appears to be effective and safe in patients with sinus node disease(41) .

Patients with isolated sinus node disease should, ideally, never require to pace in the ventricle, and thus should be protected from the effects of right ventricular pacing. Where there is co-existing AV node disease, dual chamber devices need to be employed, but these need to be appropriately programmed to minimise unnecessary pacing the ventricle.

5.9 Pacing in AV node Disease

Patients with pure atrio-ventricular node disease require a pacemaker to “track” intrinsic atrial activity and deliver ventricular pacing where intrinsic AV nodal conduction does not occur.

5.9.1 Identifying at risk patients

The vast majority of previous studies demonstrating excess detrimental clinical effects of right ventricular pacing have been performed in patients with impaired left ventricular systolic function. As previously discussed there are many potential ill-effects of right ventricular apical pacing, the long-term significance of which is not yet completely understood. Whilst a reduction in ejection fraction of 6% (from 60%) may be inconsequential to an normal person, in an individual with heart failure and an EF of 20% any fall in EF may translate to a deterioration.

5.9.2 Pacemaker programming

The requirement for ventricular pacing in AV node disease is often intermittent. Patients with second degree AV block, for example, only require pacing in the ventricle in the absence of an intrinsic QRS, furthermore patients with complete AV block often have intermittent AV nodal conduction. There is a balance to be achieved between providing necessary ventricular pacing at a physiological AV delay, and avoiding unnecessary pacing. Pacing algorithms are available that can discriminate first and second degree AV block, only delivering pacing in the ventricle during periods of high degree AV block(86, 87). In unselected patients one such algorhythm AAIsafeR (Sorin group) was shown to significantly reduce ventricular pacing (9 ± 21% v 95 ± 14%) when compared to conventional DDD programming. Importantly no adverse events were noted

this population , in particular there were no episodes of syncope, pre-syncope, light-headedness, or reported palpitation(88). Other manufacturers have produced similar algorhythms with similar results (89)

Thus in patients with intermittent AV nodal conduction it may be reasonable to use such algorithms usually used to reduce ventricular pacing in sinus node disease. This strategy would allow the physician to program a physiological AV delay, whilst allowing the device to look for an intrinsic rhythm if present, and thus minimising the extent of pacing in the ventricle and the potential for the associated deleterious effects. In the ADAPTA (Medtronic) study, individuals with AV block and sinus node disease received a pacemaker with the managed ventricular pacing (MVP) algorhythm. This algorhythm permits up to 2 out of 4 atrial impulses to fail to conduct to the ventricle prior to instigating ventricular pacing. Milasionovic and colleagues reported an impressively low percentage pacing in the AV block group (28.8%) suggesting that these algorhythms may well have a role to play in AV node disease.

5.9.3 Alternative Pacing Sites within the Right Ventricle

A pacing impulse delivered high on the ventricular septum, near the RV outflow tract (RVOT), or near the anatomical His bundle may be advantageous by allowing distal electrical conduction using the patients' His-Purkinje system, thereby reducing dyssynchrony. Pacing the His-Purkinje system directly approximates normal conduction closest, and this has been the subject of several small trials (90-92). Although the results are encouraging, the most recent study (92) suggests his or para-hisian pacing is achievable in 85% of

cases, the procedures are technically challenging, requiring specialist implant tools and skills and concludes that further larger and longer follow-up studies would be required prior to widespread adoption.

A quantitative review of RVOT pacing by De Cock *et al* (93) reviewed 9 studies comparing apical with RVOT lead placements in man. However, only two of these studies reported long term haemodynamic improvements with the other 7 providing only acute haemodynamic data. Nevertheless the authors concluded that RVOT pacing may confer a modest but significant benefit over RV apical pacing. An encouraging retrospective analysis of patients with dual chamber pacing for AV block observed a reduction in mortality in patients paced at the RVOT compared to apical pacing at 18 months (94). A further review of 460 cases supports the finding that this site offers no increased risk to the patient and no significant difference in pacing threshold, sensing, or pacing lead impedance between RV apical and RVOT leads(95, 96). Similarly, the RV mid-septum has also showed promise as an alternative pacing site, with lead placement at least as effective and safe as apical pacing(97). One short term study has suggested that dyssynchrony may be reduced by this technique; however, it would appear that this may not translate into measurable benefit in terms of B-type natriuretic peptide, LV ejection fraction, and exercise capacity (98). McGavigan *et al*, however, demonstrated the heterogeneity of septal lead placement within one single centre which may also explain the contrasting trial results(99). Multisite or bifocal RV pacing has also been explored and may be

beneficial(100), but comparative studies are lacking. Although the emerging evidence suggests that these alternative pacing sites may provide a means to avoid pacing induced heart disease, there is no clear evidence that pacing of any RV site is superior to pacing the apex.

5.10 Cardiac Re-synchronisation Therapy

CRT is defined as the stimulation of the left ventricle or simultaneous stimulation of the left and right ventricles after an atrial sensed or paced event or in atrial fibrillation.

CRT seeks to address both atrio-ventricular and ventricular (inter and intra) dyssynchrony. The concept of CRT was developed in the context of systolic heart failure where adverse outcome with prolonged QRS was established in the eighties. On the back of this concept, Lattuca and colleagues hypothesised that pacing the left ventricle in addition to the right would address the long activation time(101). In the first study of percutaneously placed cardiac resynchronisation therapy, Blanc and colleagues studied 27 individuals with systolic heart failure and broad QRS. They were able to demonstrate significant improvements in systolic blood pressure and pulmonary capillary wedge pressure (as a surrogate for LA pressure) with biventricular pacing when compared to RV only pacing or intrinsic rhythm. Two subsequent studies demonstrated that optimisation of atrio-ventricular timing with biventricular pacing offered further improvement on indices of LV function (LV dP/dt_{max}

(Figure 5.5) and pulse pressure) with optimum acute benefit seen with simultaneous LV and RV pacing at a patient specific optimal AV delay(102, 103).

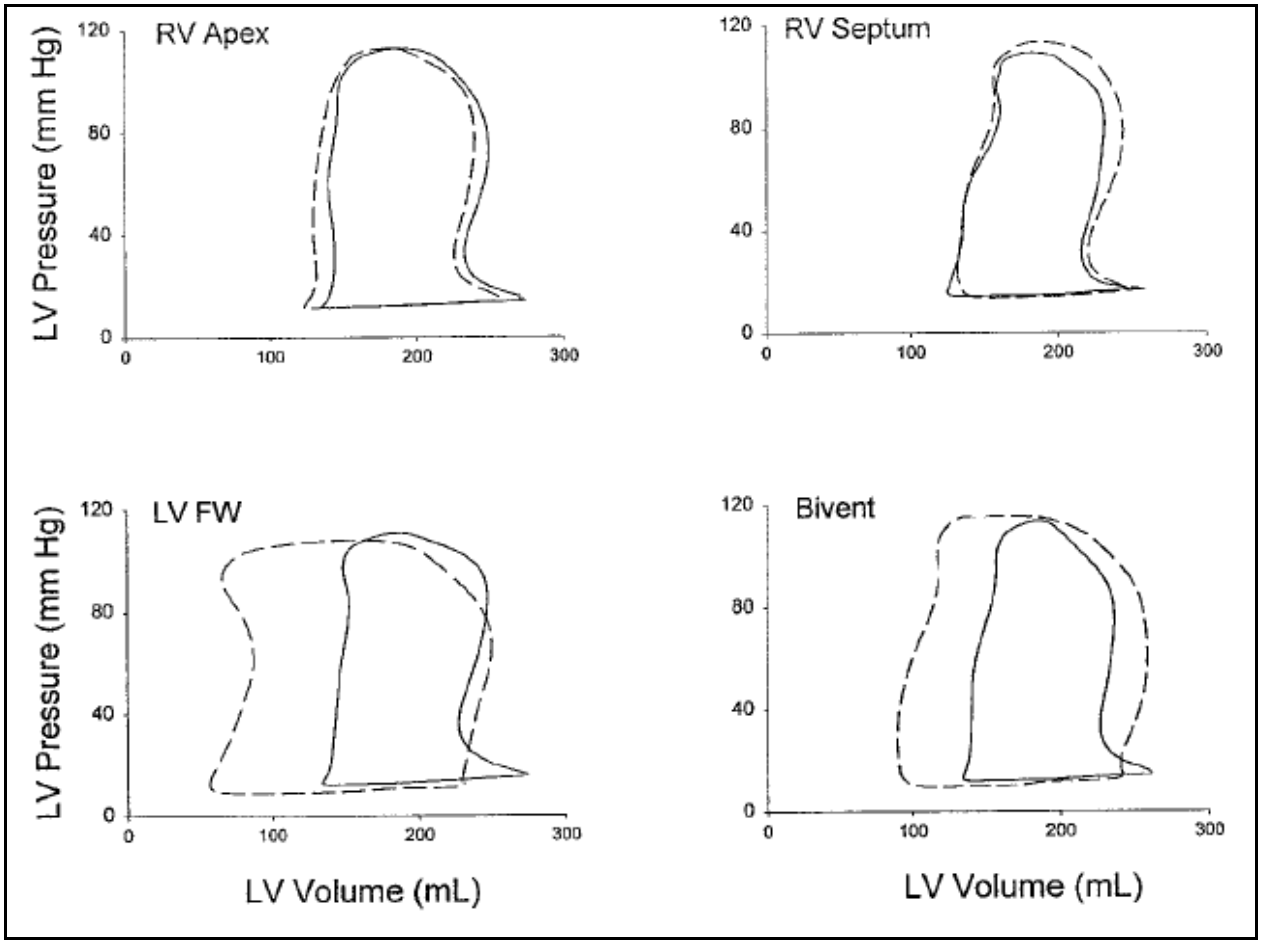


Figure 5.5 Pressure volume loops in a patient with systolic heart failure and LBBB with differing pacing sites. The solid line denotes intrinsic sinus rhythm, whilst the dashed line denotes pacing at the site specified. Note the broader loops with greater area (stroke work), width (stroke volume) and smaller LV systolic volume (increased contractile function). Reproduced from Kass et al.

These initial studies lead to large randomised controlled trials; the earliest large studies were parallel studies with patients randomised to CRT on v CRT off. CONTAK-CD(104) and MIRACLE ICD(105) included patients in sinus rhythm with NYHA II-IV and NYHA III-IV symptoms respectively with an LV ejection fraction of less than 35% and a QRS duration greater than 120 and 130 respectively. Individuals with a requirement for bradycardia support were excluded from the analysis. Table (XX) summarises the major published controlled trials investigating CRT in heart failure with prolonged QRS.

Bi-ventricular pacing is well established in guidelines for the treatment of decompensated heart failure and broad QRS without indication for conventional pacemaker insertion (106). There are, however, a significant number of patients with pre-existing LV dysfunction who require pacing for bradycardia, but do not fulfil standard indications for biventricular devices (82). These patients are the most at risk from a high burden of right ventricular pacing.

5.10.1 What evidence exists to support CRT in this context?

The Post AV nodal Ablation Evaluation (PAVE) study recruited 252 patients who were undergoing AV node ablation for atrial fibrillation and were unable to walk greater than 45m in a 6 minute hall walk test. Impaired LV systolic function was not a requirement for study entry, but 46% of patients had an LV

EF <45%. Participants were randomised to RV or biventricular pacing and followed for 6 months. Both RV and biventricular pacing improved the hall walk distance, peak oxygen consumption on cardiopulmonary exercise testing and quality of life improvement, however the improvement was significantly greater with biventricular pacing. Additionally, in patients with LVEF < 45%, there was a significant improvement in LVEF with biventricular, but not RV, pacing.

The HOBIPACE (107) study investigated the effects of using biventricular pacing, either as a de novo implant, or an upgrade of an existing RV pacemaker, to treat bradycardia in 30 heart failure patients in the absence of standard criteria for biventricular pacing. This small study demonstrated superiority of biventricular to RV pacing in respect of LV function, quality of life, and maximal as well as sub-maximal exercise capacity.

Although additional clinical evidence is limited, latest European guidelines now recommend (level IIa) consideration of biventricular pacing for such patients (108). Some studies even suggest biventricular pacing offers benefits compared to conventional RV pacing in patients with normal LV function. Yu et al(109) randomised 177 patients with bradycardia, AV node disease and normal LV ejection fraction to RV apical or biventricular pacing for 12 months. The authors reported a significant fall in ejection fraction and adverse LV remodelling in the RV pacing group only. It should be noted; however that percentage of RV pacing was high in the RV pacing group at 97%, perhaps exaggerating the benefit noted. Furthermore the study did not demonstrate any significant

difference in admissions for HF at 1 year between the groups.

In practice, whilst biventricular pacemakers may offer optimal pacing compared to conventional pacemakers, routine implantation of these devices for all patients with bradycardia is not currently feasible due to constraints on implantation time, availability of expertise and device costs. Indeed although some studies have demonstrated some impact in terms of ejection fraction, they have failed to demonstrate any clear clinical or survival benefit in patients with normal LV function. Importantly LV lead placement also entails increased radiation exposure to patients and implanters and the attendant risks thereof.

The greatest benefit of biventricular pacing is therefore likely to in those with pre-existing depressed systolic function.

5.11 Pharmacologic therapies

Ventricular dyssynchrony is strongly influenced by haemodynamic change such as afterload (110) and LV wall stress and fibrosis(111). In this respect, drugs such as angiotensin converting-enzyme inhibitors (ACEIs) that are capable of reducing afterload and left ventricular wall stress may potentially be useful in pacing induced heart disease. ACEIs reduce left ventricular wall stress, slow adverse ventricular remodelling (112) and reduce myocardial fibrosis (113). Additionally, ACEIs can modulate sympathetic activity (114), an important pathophysiological process in pacing induced heart disease. Finally, ACEI therapy reduces systemic vascular resistance and afterload and has

consistently been shown to improve endothelial function (115). However, the impact of ACEIs in pacing induced dyssynchrony has been little studied and most of these are limited to animal pacing models. Funabiki et al first demonstrated the beneficial effects of ACE-I alone or in combination reduced fibrosis and LV remodelling in a pacing model of heart failure in dogs (116). More recently, Kurita et al demonstrated diminished LV dyssynchrony during progression of heart failure in a pacing dog model when pre-treated with ACEI (117). In that study, the total systemic resistance, arterial elastance, left ventricular end diastolic pressure and myocardial collagen density were significantly lower in the ACEI treated group of dogs compared to controls. It should be stressed that all these studies were in animals, but in man, Williams et al had shown a non-statistically significant trend in AF reduction with ACEI/ARB therapy post dual chamber pacemaker implantation(118).Clearly, the findings of the potential beneficial effects of ACEIs observed in the animal studies need to be tested in patients to help define the therapeutic potential of ACEIs in pacing induced heart disease.

5.12 Summary

It would appear that pacing from the RV apex can induce dyssynchronous activation of the ventricles. Dyssynchronous activation of the ventricles has been shown to cause left ventricular dysfunction and is associated with adverse cardiovascular outcomes. The mechanisms underlying this *"pacing induced heart disease"* are not well defined. It could potentially involve sympathetic activation which can cause abnormalities in myocardial perfusion, and worsen cardiac output and endothelial function. There is thus a need to explore therapeutic strategies in pacing induced heart disease.

Biventricular pacemaker insertion seems to offer benefit in such a population, but the extent to which biventricular pacing may ameliorate the adverse effects of RV pacing remains poorly understood.

6. Research Questions and Hypotheses

Prevalence of heart failure in patients with bradycardia referred for pacemakers

What is the prevalence of impaired left ventricular systolic function in patients referred for pacemaker insertion?

I conducted an initial study to determine the population who may be highest risk for pacing induced heart disease by means of data-linkage across various datasets. This study also provided an estimation of the population from which potential studies could recruit.

The effects of right ventricular pacing on haemodynamics and endothelial function in man.

What are the potential mechanisms that may underlie pacing induced heart disease?

I hypothesised that compared to normal his-purkinje ventricular activation; RV pacing worsens cardiac output and results in abnormal neurohormonal activation and endothelial function.

I sought to examine the potentially detrimental effects of pacing the ventricle in patients with sick sinus syndrome.

Choosing the right pacing mode in heart failure

*Does biventricular pacemaker insertion ameliorate the effects of RV pacing in patients with impaired LV systolic function**?***

I hypothesised that compared to right ventricular apical pacing; biventricular pacing is associated with improved cardiac output and results in less abnormal neurohormonal activation and endothelial function.

I sought to determine whether biventricular pacing was superior to right ventricular pacing in patients with bradycardia and AV block. Specifically excluding patients who were known to benefit from Biventricular pacing this study aimed to determine whether pacing the right and left heart reduced the detrimental effects seen with right ventricular pacing alone.

The observed effects of Renin-Angiotensin system blockers in patients paced for complete atrio-ventricular block.

Do drugs which inhibit the Renin-Angiotensin system offer beneficial effects in patients exposed to a high degree of right ventricular pacing ?

I hypothesised that in patients with a high degree of right ventricular pacing; ACEI use is associated with better outcome. This study employed linkage of datasets to determine whether patients with complete av block who received a

pacemaker and were also prescribed an ACEI or ARB experienced less hospitalisation for heart failure and enhanced survival.

This thesis seeks to explore the potential hazards of right ventricular pacing and the benefits of biventricular pacing in patients with depressed left ventricular systolic function.

7. Methods

7.1 Introduction

This chapter details the generic methods used to conduct the research. The methodology is discussed in two main sections. Studies involving handling and review of datasets and a second section detailing the clinical methodology involved in each clinical study. All the measurements were performed within the department of Cardiovascular and Lung Biology within Ninewells Hospital.

7.2 Ethical Approval

- All applicable studies were considered by the East of Scotland Ethics service, and approval obtained prior to commencement.
- All subjects recruited into studies provided full written informed consent.
- All investigators held active good clinical practice certification.
- All data handling was conducted in line with the Caldicott principles and all handling of patient identifiable datasets was kept to an absolute minimum and was pre-approved by the Information and Governance officer for NHS Tayside, the Caldicott Guardian and the Chief Operating Officer of NHS Tayside.

7.3 Database Studies

Tayside has a unique collection of electronic datasets which can be deterministically linked, at the level of the individual by a unique identifier – The Community Health Index (CHI) Number. The 10 digit identifier was originally developed and implemented in Tayside in 1978(119), and has been used since as the preferred method of individual identification. This number is normally formed using the patients' 6 digit date of birth followed by four digits: two digits randomly generated to ensure a unique number, the third digit identifying gender at birth (odd for men, even for women) and a check digit. Its use has spread throughout Scotland and, in 2009, uptake of CHI number was reported to be between 96 and 99.8%(120). Without the CHI number, individuals can only be deterministically link on the basis of probability matching using name and date of birth, the added complexity of name changes, especially in the case of married females, makes this time consuming and potentially missing approximately 10% of matches(121). The presence of the CHI number throughout all electronic datasets within Tayside delivers a unique opportunity to perform observational studies with datasets that can be deterministically linked at the level of the individual (122).

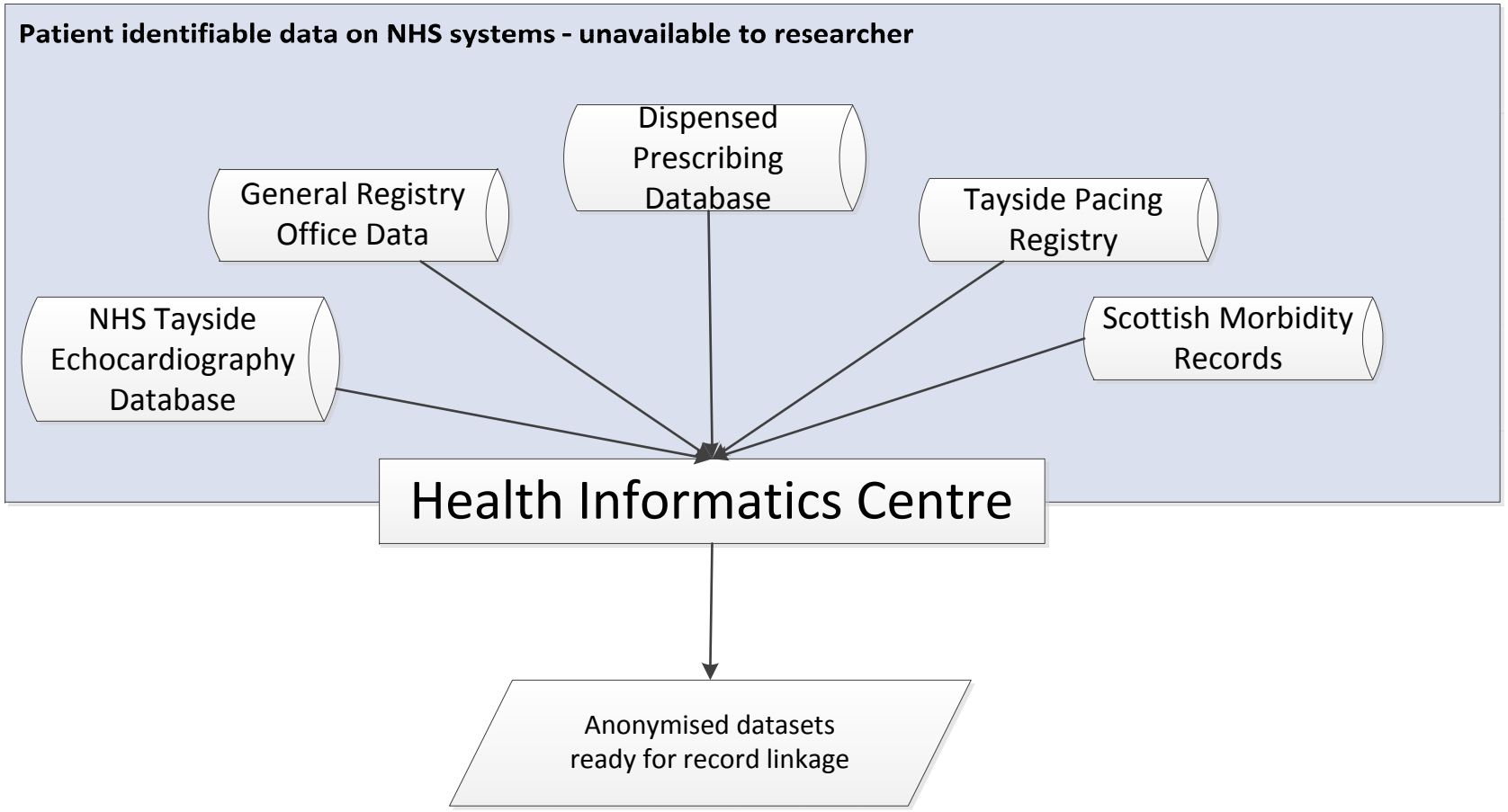
7.3.1 Management of Datasets

The importance of confidentiality necessitates the safe and sensitive handling of large datasets of patient specific data. In 1997 in England the chief medical officer commissioned a review of the way in which patient information was

handled within the NHS. Dame Fiona Caldicott published her "Report on the Review of Patient-Identifiable Information" (123)In the report she set down six clear principles i) Justify the purpose, ii) Don't use patient identifiable information unless absolutely necessary, iii) Use the minimum necessary patient identifiable information, iv) Access should be on a need to know basis, v) Everyone with access to the information should be aware of their responsibilities, vi) Understand and comply with the law. In order to comply with these principles and to conduct research in an ethical and respectful manner, the Health Informatics Centre (HIC) at the University of Dundee handles all requests for such data. HIC has in place a standard operating procedure to handle such queries which have been approved by the ethics committee in Tayside. HIC select pre-defines cohort for each research project, and provide access to an anonymised version of the data to the researcher. Data is transferred in an encrypted form using the protected NHS N3 network and is stored upon encrypted computer drives on researchers' computers.

A detailed protocol covering the intended use and storage of the data for each project was submitted to the HIC and to the cardiology data owner to provide justification and to gain permission to use the datasets. (Figure 7.1)

Figure 7.1 – Schematic to demonstrate dataflow between NHS systems and researchers.



7.3.2 Tayside Pacing Registry

Since 1994 all patients undergoing permanent pacemaker, implantable defibrillator, implantable loop recorder or cardiac resynchronisation therapy have had data pertaining to implant and follow-up stored in the Tayside Pacing Registry. Initial data at the time of implant is entered by trained physiologists and includes, but is not limited to, device type, lead type(s), date of implant, baseline implant testing details, symptoms prior to implant, ECG findings, presumed aetiology of rhythm disturbance, the latter are all recorded according to the European Pacemaker Identification card coding system. Scottish Morbidity Record 01 – (SMR01)

The Scottish Morbidity Record is a record of hospital attendance either as an inpatient or a day case. A record is created in SMR01 for every individual who is admitted to hospital and is updated on discharge, or transfer to another institution, with details of that admission including, dates of admission and discharge, admitting institution and the main condition and up to 8 ancillary conditions based upon International Classification of Diseases (ICD) 9, and more recently, ICD10 diagnostic codes. Additionally procedures performed are coded by OPCS4 (Office of Population Census and Surveys - Classification of Interventions and Procedures, version 4).

7.3.3 Echocardiography Dataset

Tayside holds data, indexed by CHI number, on a regional echocardiography database. All outpatient echocardiograms performed are reported to the requesting practitioner by using this system. Significant volumes of data including cardiac dimensions, valvular appearances and flow rates, together with a free text describing ultrasonographers' opinion of cardiac function are recorded within the dataset.

7.3.4 General Register Office for Scotland – Death Register

All deaths in Scotland are legally required to be recorded on the register. Information recorded includes date of death, together with the main cause with up to 4 contributing causes, and 2 other conditions which although not leading directly to death, were recorded as significant illnesses. All deaths are certified by physicians and data from death certificates are matched to ICD diagnostic codes as these are entered onto the electronic register.

7.3.5 Dispensed Prescribing Database

The Medicines Monitoring Unit at the University of Dundee, collects data on all dispensed prescriptions in the region. This data is indexed by CHI number and updated regularly. The data includes the date of dispensing, the drug dispensed, the formulation, quantity and the dose.

7.4 Statistical Analyses

All statistical analysis were undertaken using IBM SPSS statistics (formally SPSS) v20 (SPSS: An IBM Company), SPSS v16 (SPSS: An IBM Company) or Stata SE11 (Stata. Corporation, Texas).

7.4.1 Descriptive Statistics

Categorical Variables

Differences in categorical variables were reported using the chi square test where two populations were compared. Where a comparison of three or more populations was performed, analysis of variance (ANOVA) was utilised. These were undertaken using the ",chi" qualification for tables or "oneway" command in Stata or the compare means or ANOVA function in IBM SPSS.

Continuous Variables

Prior to analysis the distribution of each variable was examined. Normally distributed data was presented as mean ± standard deviation, whilst non-normally distributed data was presented as the geometric mean ± inter-quartile range or median and range as appropriate.

Differences in populations were determined by paired t-test for normally distributed, paired data and unpaired t-test where data was unpaired. Non-normally distributed data was assessed by the non-parametric mann-whitley U test or ANOVA as appropriate.

7.4.2 Interaction between study arms

In order to account for any potential interaction occurring as a result of the order by which the subjects received each pacing mode, a mixed model linear regression analysis was employed to determine, and adjust for, the presence of any such interaction.

The study arm and the period during which this was recorded were entered as centred co-variants, encoded as -0.5 and +0.5. A further interaction term was included as the product of the two and all were entered into the model as fixed effects.

7.4.3 Survival Analyses

Statistical modelling of survival was undertaken using the Kaplan Meier and Cox's proportional hazards regression(124) methods.

7.4.3.1 Cox's Proportional Hazards.

Cox's model for assessment of proportional hazards over time was used to determine the effect of different co-variants on outcome in a studies population. The mathematical model as originally conceived enables the calculation of the effect on a measured variable on the outcome, assuming the co-variants are, or are assumed to be, multiplicatively related to the hazard (125).

When survival analyses were undertaken using Cox's proportional hazards model, the assumptions of the model were checked by graphically assessing Schoenfeld residuals (differences between the values of an individual's covariates at failure and the risk-weighted mean covariates for those at risk) . Furthermore the 'phtest' command in stata permits a chi squared test to determine whether the assumptions of the proportional hazards model are met.

7.4.3.2 Time dependent analysis

Where the variables of interest changed during the follow-up period with respect to others in the population a time-dependent analysis was performed to minimise the potential for immortality bias(126).

Immortality bias is particularly relevant where drug therapy is being considered and can occur where one group “must survive” e.g. in order to get treatment. To take an example; a retrospective study is performed and shows that professors live longer than their no-professorial colleagues. In this study if an individual is currently in a non-professorial position and due to become a professor in the next year but dies they will be considered in the non-professorial group (even though they were destined to become a professor). Professorship is thus associated to those who are older and thus given immortality bias.

To account for this in longitudinal analyses, time varying variables were employed. Given the immense computing power required to consider changes in variables each day for each individual time dependent, variables were permitted to change at 30 day intervals during the at risk period. 30 days was considered appropriate given this was approximately the minimum length of time for a cardiovascular drug prescription. Using stata the baseline datasheet was expanded to provide a single data row for each 30 days the individual was considered at risk and variables were specified according to whether prescription for drug had occurred.

7.4.4 Compliance

Where the effect of drug prescription upon outcome was studied an overall measure of compliance was estimated. Compliance was determined by calculating the mean of the intended duration of therapy for each prescription expressed over the interval of days until the next prescription was issued. If subsequent prescriptions were issued before the end of a previous prescription censoring of the previous prescription occurred, thus maximum adherence was 100%.

7.5 Clinical Study

7.5.1 Cardio-pulmonary exercise testing

I measured Cardiac Output non-invasively using the inert gas rebreathing technique (Innocor, Innovision A/S, Odense, Denmark).

After 30 minutes of bed rest patients breathed in N2O (blood soluble gas) and SF6 (blood insoluble gas) at concentrations of 0.5% (V/V) and 0.1% (V/V) respectively through the Innocor rebreathing system. This oxygen enriched mixture, 28% O2 (V/V) in a pre-filled 3L anaesthesia bag formed a closed circuit with the patient's respiratory system. Photoacoustic analysers measured changes in gas concentrations over a 5-breath interval, with 2 required to perform a successful analysis.

The N2O concentration decrease was proportionate to pulmonary blood flow (PBF)

and SF6 concentrations allowed for the measurement of the total volume of the closed system, after equilibrium was reached. Measurements of O2 provide VO2 results.

PBF = CO in the absence of pulmonary shunt defined as an arterial O2 saturation of >98% measured by pulse oximetry.

A standard exercise bicycle (Ergoline, ergoselect 100P) protocol was used. Stages lasted 3 minutes starting with 0 watts, resistance was increased by 25 watts after each stage. (Figure 7.2)

Rebreathing tests were done at rest, 50 watts and patients were asked to indicate a minute before terminating exercise to allow for the measurement of peak exCO.

The inert rebreathing gas method has been validated against the invasive gold standard, where blood flow is measured from the pulmonary artery with a Swan-Ganz thermodilution catheter and it has been validated for use in many study populations. (127-129)

It is easily performed and well tolerated by patients(130).

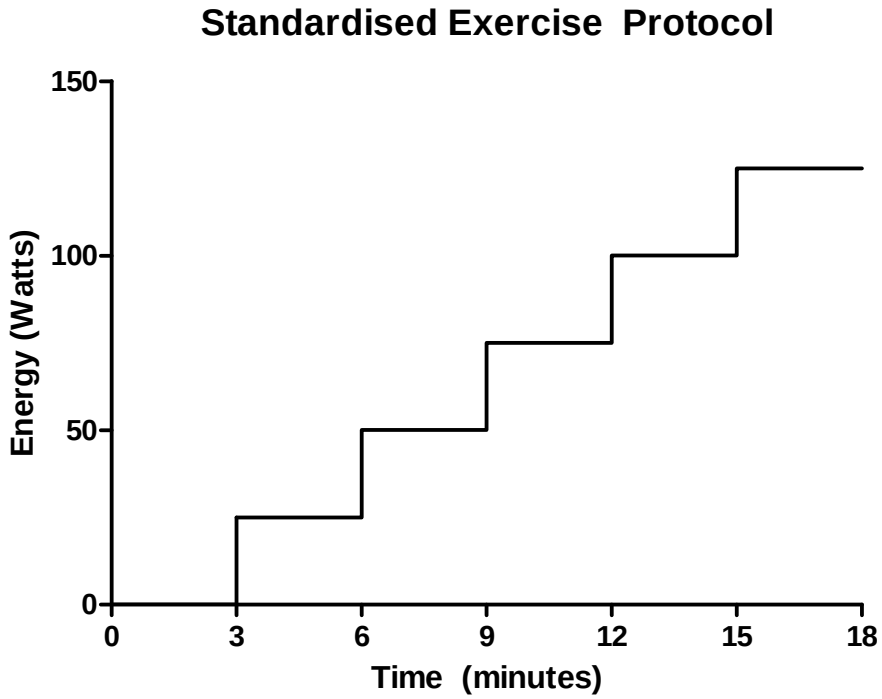


Figure 7.2 – Standardised exercise protocol using the Innocor system.

7.5.2 Endothelial Function

I assessed endothelial function non-invasively using the ENDO-PAT system (Itamar Medical Ltd, Caesarea, Israel). Individuals were asked to fast, drink only water and avoid nitrate medication in the 4 hours prior to testing. Testing was performed after 30 minutes of rest in a quiet neutral environment, air conditioned at 21^{o}C. Probes were placed on the index fingers of each hand and the arm supported from the elbow on a foam support. A rapid inflation blood pressure cuff was placed over the brachial artery on one arm (Hokanson E20 rapid cuff inflator).

Baseline measurements were taken for > 5 minutes, the cuff was inflated to the higher of 200 mmHg or 60 mmHg above systolic pressure with a maximum of 300 mmHg to ensure complete occlusion and left inflated for 5 minutes. This provided the consistent ischaemic stimulus for flow mediated dilatation induced post-occlusion. The cuff was then rapidly deflated and the resultant reactive hyperaemia was assessed for > 5minutes. (Figure 7.3)

The endothelial function was determined independently of the investigator. The RH-PAT index was calculated as the ratio of the average amplitude of the PAT signal over a 1-min time interval starting 1 min after cuff deflation divided by the average amplitude of the PAT signal of a 3.5-min time period before cuff inflation (baseline). Subsequently, RH-PAT index values from the study arm were normalized to the control arm controlling for systemic responses such as

sympathetic activation(131).

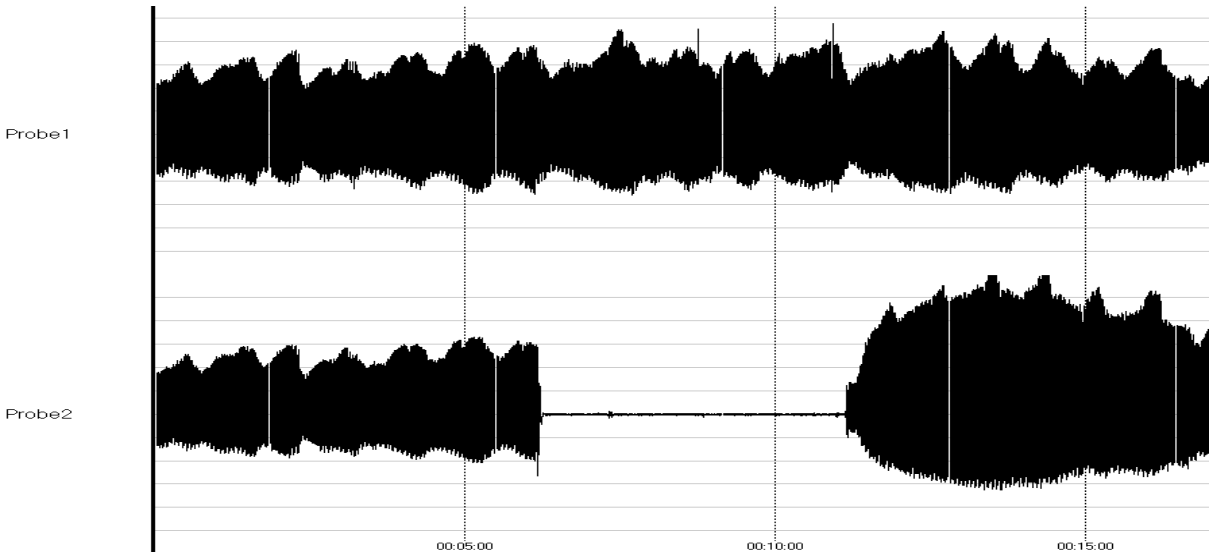


Figure 7.3 – Normal response seen with post-occlusive hyperaemia seen in the study arm (Probe 2)

7.5.3 Echocardiography

Echocardiography was performed on a Phillips IE33 ultrasound system by one of my colleagues within the echocardiography room in the department of clinical pharmacology. Given standard echocardiography requires the use of an ECG rhythm strip, and sight of this may lead to potential un-blinding, echocardiography was performed by an independent blinded physician trained in echocardiography, according to a standard protocol. The scans were analysed and measured “offline” by 2 independent trained reviewers, who were also blinded to the study arm. The mean of measurements obtained by the two reviewers were taken forward for analysis.

Participants were asked to position themselves in the left lateral position and

the couch angled to 30^{o}.

The standard protocol included storage of a video clip comprising 3 cardiac cycles in the each of the standard echocardiographic planes including parasternal long axis, parasternal short axis, apical 4 chamber and apical 2 chamber. Continuous wave doppler studies through the Aortic and Pulmonary valve were also recorded.

Simpsons biplane method(132) was utilised to estimate the ejection fraction, and timing.

All studies were electronically stored on a secured archive system identified only by study ID and visit number.

7.5.4 6 minute un-encouraged hall walk test

I undertook 6 minute hall walk tests as a submaximal test of exercise capacity which correlates with peak oxygen consumption. Exercise capacity is a powerful independent predictor of prognosis in heart failure, and also influences health-related quality of life. The 6MWT has been shown to be sensitive to change in response to exercise interventions in older people with a variety of conditions(133). Although peak oxygen consumption is an established marker for medical and device interventions and for assessment of exercise capacity in CHF(134), we anticipate that in this study population, peak exercise may be difficult to achieve due to reduced patient motivation, unable

to use the mouthpiece, or cycle. Therefore the 6MWT which is a submaximal test and less subject to this limitation was chosen as the primary end point for the choosing the optimum pacing mode in heart failure study. The 6MWT was performed using a standardised approach over a 25 metre course. Subjects were permitted to use their usual walking aids and were given standard advice at the start of each test. They were advised:

i) To repeatedly walk back and forth along the course

ii) No time warnings will be given

iii) They should aim to walk as far as they could during the 6 minutes.

They were permitted to rest if they felt this was required, and chairs were placed along the course to facilitate this. The investigator stood at the half way point of the course such that an accurate distance might be measured. Time was allocated on a count-down stopwatch and a sound denoted the end of the test. Total distance achieved was noted at each test.

7.5.5 Blood Pressure

I measured blood pressure using an Omron automatic osciilometric blood pressure monitor (Omron 7051T). Readings were obtained twice and if these differed by > 10 mmHg, a further 2 readings were obtained with a manual sphygmomanometer.

7.5.6 Blood hormone sampling

7.5.6.1 Venepuncture

I or my research assistant performed Venepuncture on a peripheral vein using tourniquet to promote venous filling. Samples were collected using the vacutainer system. Analysis of all hormone levels was performed by Mrs Lesley MacFarlane in the Department of Cardiovascular and Lung Biology, in Ninewells Hospital, Dundee according to the departmental protocols.

7.5.6.2 Plasma Brain naturetic peptide (BNP)

A 7 ml purple vacutainer containing potassium EDTA was collected during venepuncture. Immediately after filling, the sample was immediately placed on ice. The sample was subsequently centrifuged as soon as possible for 10 minutes at 3000 rpm in a temperature controlled centrifuge at 4^{o}C. The Plasma was then pipetted into a 5ml sample container, labelled, then stored at -70^{o}C, until analysis.

BNP levels were assayed using Bachem radioimmune assay kit (Bachem, Peninsula Laboratories, Inc, US).

7.5.6.3 Highly sensitive c reactive protein

A 7 ml golden vacutainer was collected during venepuncture. Approximately 30m minutes after filling the sample was centrifuged for 10 minutes at 3000 rpm in a temperature controlled centrifuge at 4^{o}C. The serum was then

pipetted into a 5ml sample container, labelled, then stored at -70^{o}C, until analysis.

7.5.7 Questionnaires

Studies used both a generic health questionnaire (The EuroQol) and a disease specific questionnaire (Minnesota Living with Heart Failure). Both questionnaires were completed by the subject in the study without external assistance. Subjects were asked simply to follow the instructions and record their responses. Questionnaires were checked on completion to ensure no omissions. The questionnaires are included as appendices in this thesis.

7.5.7.1 EuroQol Questionnaire (Visual Analogue Scale)

The EuroQol was initially developed in 1987 as a standardised disease independent instrument for assessing quality of life. (135) It has been extensively validated in the general population and different disease groups(135-137) and proven to be a reliable measure. In particular, the EuroQol has been shown to be useful in assessing patients in whom a significant change in health status is expected, and consequently it is useful to measure response to intervention. (138)

The EuroQol is a generic health questionnaire designed to assess overall wellbeing, health and functional status. The study used the visual analoque scale, upon which subjects are asked to mark where they felt their own “health state today” lay. The scale is annotated between 0 and 100 with 0 being the

“worst imaginable health state” and 100 being the “best imaginable health state”. The point marked was recorded as a score between 0 and 100.

7.5.7.2 Minnesota living with heart failure questionnaire.

The Minnesota living with heart failure questionnaire is a disease specific questionnaire designed to assess the impact of heart failure as a disease and its treatment on an individual’s quality of life(139). It has been extensively validated (140) and is straight forward to use.

7.6 Power & sample Size Calculations

Power calculations were completed at the time of study design to estimate sample size and are described in each chapter as appropriate.

7.7 Data Entry and Management for clinical studies

Data was entered during study visits onto a structured case report form by either DE or a research assistant trained in good clinical practice. Given the need to maintain blinding, and the fact that the echocardiogram would produce an electrocardiogram trace which may in turn declare which arm of the study the patient was currently in, the echocardiograms were performed by an independent physician and archived. The scans were all reported at study end and the results entered onto the case report form prior to un-blinding.

Data was entered into a secure Microsoft Excel spread sheet with individuals identified only by study ID, was encrypted and stored on a secure university server.

8. Prevalence Of Heart Failure In Patients With Bradycardia Referred For Pacemakers: Cost Implications of Primary Biventricular Pacemaker Implantation.

8.1 Introduction

Pacemaker implantation remains the only therapeutic option that improves morbidity and mortality for patients with symptomatic bradycardia. However, pacing from the right ventricular apex can induce dyssynchronous activation of the ventricles, reduce left ventricular (LV) ejection fraction and increase LV end systolic volume, and thereby may lead to worsening heart failure(3, 7, 141, 142). Previous studies have demonstrated that, in patients with conventional right ventricular pacemakers and significantly impaired left ventricular systolic function, upgrade to biventricular pacemakers, improved left ventricular ejection fraction, exercise capacity and quality of life at 3 months(107). Although current pacemakers have pacing algorithms to minimise right ventricular apical pacing, patients with atrio-ventricular disease are still at risk at pacing induced ventricular dyssynchrony. As such, guidelines form the European and American cardiac societies recommend consideration of implantation of biventricular pacemakers with the aim of avoiding chronic right ventricular pacing in heart failure patients who already have left ventricular systolic dysfunction(108). However, routine primary implantation of biventricular pacemakers in patients with class I bradycardia indications for pacing and with pre-existing heart failure from left ventricular dysfunction (but without indications for cardiac resynchronisation therapy), has significant cost and health resource implications which cannot be reliably estimated at present, as the prevalence of heart failure or left ventricular dysfunction in the

population being referred for pacemaker implantation is unknown. A previous study reported the prevalence of heart failure in patients seen in a pacemaker follow up clinic, but this is included patients who developed heart failure post implantation (82). Therefore the aim of this study was to determine firstly the prevalence of pre-existing symptomatic heart failure due to left ventricular systolic dysfunction in patients with bradycardia referred for pacemaker implantation and secondly, the projected additional costs associated with using biventricular pacemakers at the time of initial implant in these patients.

8.2 Objectives

The aim of this study was to determine the prevalence of pre-existing heart failure in patients with bradycardia referred for pacemaker implantation.

The study also sought to explore the additional economic costs associated with primary implantation of biventricular pacemakers in these patients was also determined.

8.3 Ethical Approval

The study was approved by the Tayside Committee for Medical Research Ethics (ref 05/S1402/46).

The study was approved by the Tayside Caldicott Guardian.

This data used in this study was approved for release by the Tayside Cardiology IT sub-group.

8.4 Methods

8.4.1 Study Population

All patients, over the age of 18 years, receiving their first standard permanent pacemaker for bradycardia between 2000 to 2009 were included in the study. Individuals receiving multisite ventricular pacemakers, defibrillators or loop recorders were excluded. Over this period, patients received biventricular pacemakers for heart failure indications and not for bradycardia indications.

8.4.2 Study Design

This was a retrospective data-linkage observational study. Cases were identified from the Tayside Pacemaker Registry and deterministically linked at the level of the individual across other datasets in the region.

The datasets used in this study, which have been discussed and detailed previously include:

- Tayside Pacing Registry
- Tayside Echocardiography Database
- Scottish Morbidity Record
- General Registry Office – Death Certification
- Tayside Dispensed Prescription data

Access to the resulting anonymised research dataset was administered by the Health Informatics Centre at the University of Dundee using protocols approved by the East of Scotland Research Ethics Committee.

8.4.3 Definitions

8.4.3.1 Left ventricular Dysfunction

The presence of left ventricular dysfunction was determined by the most recent echocardiogram prior to pacemaker insertion. All echocardiograms were performed by accredited sonographers and significant LV dysfunction was defined either quantitatively as a left ventricular ejection fraction of <40 %, or qualitatively when described as moderate to severe.

8.4.3.1 Heart Failure

Criteria for heart failure was designed to be robust and therefore required evidence of a previous hospital admission systolic heart failure (ICD code 428.2), or documented left ventricular systolic dysfunction on echocardiography combined with repeated prescription for a loop diuretic.

This definition of heart failure using these criteria in the Tayside registry was validated separately and is currently being prepared for publication.

8.4.4 Statistical Analysis

All statistical analyses were performed using Stata (SE) version 11.1 (Stata Corp Texas).

Categorical data were analysed by the chi-square test and continuous variables by t-test or the non-parametric Mann-Whitney U test as appropriate. Results are presented as mean ± standard deviation for normally distributed data and geometric mean ± 95% confidence intervals for non-normally distributed data.

A p value of 0.05 was considered statistically significant.

8.4.5 Cost Analysis

Hospitalisation costs (including healthcare professional, pharmacy and laboratory costs) to the National Health Service in Scotland until November 2010 (latest available) were extracted from the Information Services Division Scotland (NHS National Services Scotland). Pacemaker costs ((Scottish National Pacemaker Tariff) for the corresponding period 2009- 2010 were obtained from the Scottish National Procurement Office, and the averaged suppliers' costs was used in a comparative cost analysis. We determined the average NHS purchase price for each type of device and compared this to the cost of the alternative biventricular device, additionally we also calculated the excess personnel and theatre time required to complete the procedure and determined the difference in cost that would be incurred to the National Health Service, had these patients undergone primary biventricular pacemaker implantation.

8.5 Results

8.5.1 Population

A total of 1970 patients (57% male), mean age 75 ±14 years, underwent permanent pacemaker insertion during the 10 year period. 368 (19%) were identified as having systolic heart failure using the pre-defined criteria of either: usage of loop diuretic at the time of implant combined with impaired left ventricular systolic function on echocardiography or prior hospitalisation with

systolic heart failure. Importantly, 62% of these patients had AV node disease being the underlying indication for pacing. In patients in whom echocardiography was available, In the cohort with previous echocardiography, 248 (22%) had asymptomatic left ventricular dysfunction on echocardiography without evidence of heart failure.

The characteristics of the population and their conduction disturbance are shown in Table 8.1

Table 8.1 – Population Characteristics

	ALL	Heart Failure	Non-Heart Failure	P
Number	1970	368 (19%)	1602 (81%)	
Age at implant	75 ± 14	76 ± 12	74 ± 14	0.10
No. Male	1114 (57%)	230 (63%)	884 (56%)	0.002
Diabetes	408 (21%)	116 (32%)	292 (18%)	<0.001
Ischaemic Heart Disease prior to implant	596 (30%)	230 (63%)	366 (23%)	<0.001
Echocardiography performed prior to implant	1126 (58%)	308 (84%)	818 (51%)	<0.001
Pacemaker Type				
Dual Chamber	1282 (65%)	207 (56%)	1075 (67%)	<0.001
Ventricular Based	669 (34%)	159 (43%)	510 (32%)	<0.001
Atrial Based	19 (1%)	2 (1%)	17 (1%)	<0.001
Conduction Defect				
Sinus Node Disease	866 (44%)	141 (38%)	725 (45%)	<0.001
Atrio-ventricular Node Disease	401 (20%)	111 (30%)	290 (18%)	<0.001

Atrial Fibrillation	703 (36%)	116 (32%)	587 (37%)	<0.001
Drug Therapy prior to implant				
Aspirin	1135 (58%)	307 (83%)	828 (52%)	<0.001
Beta-blocker	994 (50%)	275 (75%)	719 (45%)	<0.001
ACE	881 (45%)	316 (86%)	565 (35%)	<0.001
Digoxin	311 (16%)	144 (39%)	167 (10%)	<0.001
Loop diuretic	803 (41%)	368 (100%)	435 (27%)	<0.001
Spironolactone	274 (28%)	175 (48%)	99 (6%)	<0.001

8.5.2 Outcomes

Not unexpectedly there were significantly more patients presenting following pacemaker implant with heart failure requiring hospitalisation in the heart failure group at 2 years post implant (28% v 3% p=<0.001).

Similarly the 2-year post implant mortality rate was significantly greater in the heart failure group (45% v 13%) (Figure 8.1).

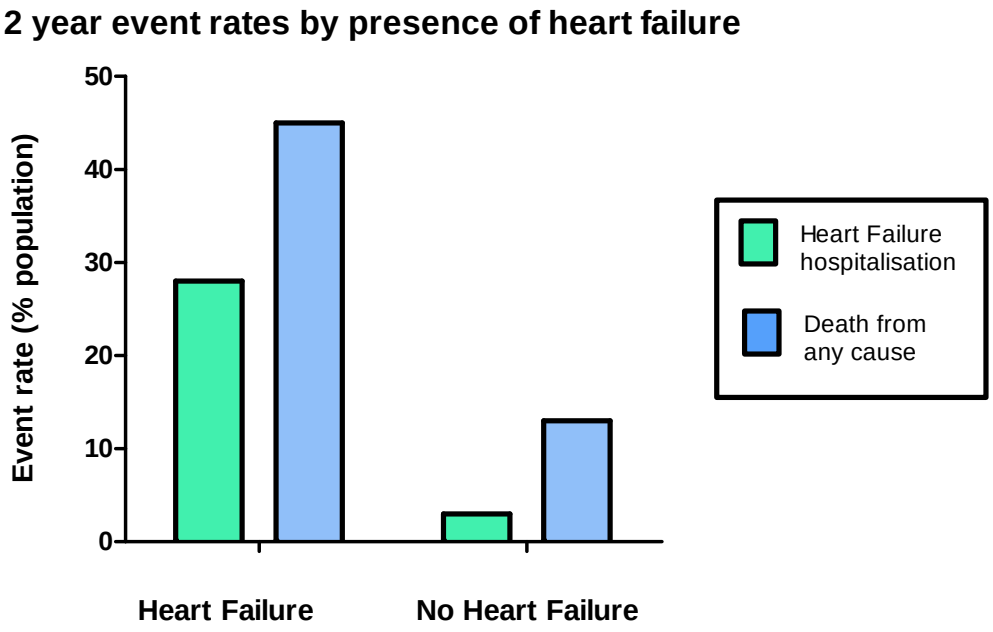


Figure 8.1 – Outcomes by presence of heart failure.

8.5.3 Cost analysis

The costs associated with the extended implant procedure times for a biventricular pacemaker relative to a dual chamber pacemaker are shown in table 2. Using the Scottish National Pacemaker Tariff for 2009-2010, the cost of

a biventricular pacemaker system offset against the cost of a dual chamber pacemaker and a VVI pacemaker was an additional £2500 (2907 EUR), and £3500 respectively. We thus calculated the total additional cost to implant a biventricular pacemaker instead of a dual chamber or VVI pacemaker to be £3468 (4023EUR), and £4468 (5183EUR) respectively, for each patient. In contrast, the average gross cost to the National Health Service in Scotland for an acute hospitalisation in 2009-20010 was £3,517 (4080EUR) per average admission of 3.4 days, i.e. £818 a day (948 EUR) (ISD Scotland National Statistics release, 30th November 2010) (Table 8.2) .

Table 8.2 – A breakdown of the additional costs associated with biventricular pacemaker insertion.

Resource	Quantity	Cost (Euro)
Theatre Hours	0.45	£264 (306)
Consultant Time	1	£611 (709)
Physiologist Time	0.45	£32 (37)
Radiographer Time	0.45	£61 (70)
Device Cost		
DDD	1	£2500 (2900)
VVI		£3500 (4060)
Total Excess Cost		
DDD		£3468 (4023)
VVI		£4468 (5183)

8.6 Discussion

This study reports the prevalence of systolic heart failure in patients referred for pacemakers for class I bradycardia indications, and assesses the cost implications associated with primary implantation of a biventricular pacemaker. In this study cohort, a striking 19% of all patients referred for pacemakers were found to have pre-existing heart failure, as defined by loop diuretic use with LV systolic dysfunction on echocardiography; or previous hospitalisation for systolic failure and therefore, according to current guidelines, should be considered for biventricular pacemakers at initial implant. Furthermore, an additional 12% had asymptomatic LV dysfunction on echocardiography and may also be at risk from developing symptomatic heart failure following right ventricular pacing, which has been shown in one study to significantly reduce ejection fraction by 7% after one year, in structurally normal hearts (14). In pre-existing left ventricular dysfunction, this reduction of left ventricular ejection fraction is likely to have a more profound deleterious impact on development of heart failure symptoms. Therefore, although at present the pacing recommendations in asymptomatic left ventricular dysfunction are not defined, this group may also benefit from primary biventricular pacing (14, 15).

Not unexpectedly, those identified as having heart failure, were older and had a higher prevalence of diabetes, ischaemic heart disease and cardiovascular drug use prior to pacemaker implantation; 86% were receiving ACE inhibitor therapy and all were taking loop diuretics. There was higher use of dual chamber devices in the non-heart failure group (67% v 56%) whilst the heart

failure group had more VVI devices. This was not due to underlying atrial fibrillation which was present in 32% of the heart failure group compared to 37% in those without heart failure. Importantly, heart failure was associated with significantly more frequent AV node disease (30% versus 18%, $p<0.001$), and therefore heart failure patients are more likely to be exposed a higher burden of right ventricular pacing.

Although there have been no studies reporting the incidence of left ventricular dysfunction and heart failure in the pre-implant population, the results are concordant with previous studies that examined the prevalence of heart failure in patients with in-dwelling pacemakers attending follow-up (82, 143). Thackray et al studied 307 pacemaker patients attending a regional pacemaker clinic and reported a higher incidence of heart failure of 27 %, with asymptomatic left ventricular dysfunction in a further 4%. In fact, the authors speculated that their observed heart failure prevalence could in part be due to the chronic effects of right ventricular pacing itself.

8.6.1 What are the potential benefits in biventricular device implantation in this group?

Several studies have demonstrated pacing from the right ventricular (RV) apex can induce dyssynchronous activation of the ventricles, reduce left ventricular (LV) ejection fraction and increase LV end systolic volume, and thereby may lead to worsening heart failure in the presence of significant burden of RV pacing. Worse cardiovascular outcomes are associated with increased frequency of RV pacing (7-9) and the degree of ventricular dyssynchrony induced (10). The DAVID study comparing dual chamber pacing at 70 b.p.m. to ventricular only back-up pacing at 40 b.p.m. in patients with significant heart failure and implantable defibrillators in situ, showed a significant increase in mortality and heart failure hospitalisations in those with >40% ventricular pacing, irrespective of pacing mode{Wilkoff, 2002 #396}. In parallel, as the benefits of biventricular pacing have been demonstrated in systolic heart failure with ventricular dyssynchrony associated with left bundle branch block (11, 12) there has been a wider recognition of 'pacing induced heart disease' caused by acquired dyssynchrony from right ventricular apical pacing. Biventricular pacing has been shown to be superior to RV apical pacing in patients with pre-existing heart failure in the HOBIPACE study{Kindermann, 2006 #175}. This crossover study compared 3 months RV only pacing to 3 months biventricular pacing and demonstrated improved left ventricular size and ejection fraction, improved exercise capacity and quality of life in the biventricular period. Furthermore biventricular pacing also appears to be better

than conventional RV pacing in patients with normal LV function. Yu et al(109) randomised 177 patients with bradycardia, AV node disease and normal LV ejection fraction to RV apical or biventricular pacing for 12 months and demonstrated conventional right ventricular apical pacing resulted in adverse left ventricular remodelling and in a reduction in the left ventricular ejection fraction; these effects were prevented by biventricular pacing, and were maintained after 24 months(144) of biventricular pacing.

8.6.2 What are the cost implications of biventricular implants for this group?

The additional cost per patient for a primary uncomplicated biventricular pacemaker implant relative to a dual chamber pacemaker was estimated to be £3465, however when offset against more than one subsequent heart failure hospitalisation, this cost is negative. Furthermore, in circumstances when symptomatic or worsening heart failure develops, the cumulative costs and attendant risks to the patient associated with a second procedure to upgrade to a biventricular pacemaker, would also favour primary biventricular pacemaker implantation. The additional risks to the patient of a second procedure to upgrade to biventricular pacing are significant. In a prospective registry study of procedural complications in 1744 patients undergoing pacemaker and ICD generator replacements, highest complications (18.7%) including death were associated with upgrade to CRT devices(145). In contrast,

the peri-procedural risks of a primary CRT implant are reported to be similar to that seen with conventional dual chambered pacemakers (146)

There is little data regarding the incidence of worsening heart failure following right ventricular pacing in patients with left ventricular dysfunction, however the MUSTIC trial of biventricular pacing in patients with NYHA III heart failure and QRS>150 ms, reported a 31% incidence of heart failure hospitalisation after right ventricular pacing, with a 70% reduction in hospitalisations associated with biventricular pacing, over a three month follow up(147). It should be noted, however, that the MUSTIC study population were a high risk group, and did not have bradycardia indications for pacing. Nevertheless, the average cost of a generic medical admission to the National Health Service in Scotland was estimated to be £3,517 in 2010, but a heart failure admission to a high dependency specialist cardiology service is likely to be greater(148) in actual terms. As such, over the lifetime of the patient, reduction by more than one heart failure admission could offset considerably the initial cost at implant.

8.7 Limitations

We used retrospective data to perform our analysis, which has it attendant limitations. It is possible that the prevalence of heart failure has been under represented in our data, as patients treated for clinical heart failure with diuretics but without echocardiographic evidence or hospitalisation would not have been included. However, strict definitions for heart failure were used in this study to ensure we identified true positives only. Furthermore, the prevalence of heart failure we have found is comparable to other studies, suggesting that bias is limited. We did not have accurate data in this bradycardic population on the prevalence of NYHA class at baseline, or on follow-up. In addition, the cost associated with subsequent complications related specifically to biventricular pacemakers, e.g. left ventricular lead displacements requiring lead re-manipulation; which is reported to be 6.6% at 11month follow-up, were not included. We performed our cost analysis based on the Scottish national tariffs in 2009-10, and therefore this may vary from current actual costs to individual hospitals and health authorities and according to inflationary effects. Similarly if implantation of biventricular devices were to be extended to all patients with bradycardia and heart failure, it is likely that the tariff cost of these devices would fall, further reducing the cost margin. Furthermore we did not take in account the costs and risk borne by patients, in particular that of extended procedures or repeat procedures to upgrade.

8.8 Conclusions

The prevalence of heart failure in patients with bradycardia referred for pacemaker implantation is significant. AV node disease is significantly higher ($p< 0.001$) in this group of patients and thus they may be at increased risk of developing worsening heart failure after conventional right ventricular pacemaker implantation and should be considered for biventricular pacing at initial implant, as upgrade procedures are associated with higher risk Furthermore, subsequent healthcare cost savings potentially offset the initial additional costs of a primary biventricular pacemaker implantation.

9. The effects of right ventricular pacing on haemodynamics and endothelial function in man.

Paper published as :

Right ventricular pacing impairs endothelial function in man.
Europace. 2011 Jun;13(6):853-8. Epub:2 011 Feb 22.

This study was conceived by Dr. Anna Maria Choy, study visits were conducted by Mr. Henry Su who also aggregated the data. Data analysis, reporting and discussion was conducted and authored by Dr. Douglas Elder**.**

9.1 Objective

The aim of this study was to investigate the potential mechanisms for the deleterious effects which may be observed with right ventricular pacing.

Specifically this study aims to determine the effects of right ventricular pacing on measures of cardiovascular performance, namely:

Resting Cardiac Output (rCO)

Exercise Cardiac Output (exCO)

Peak Oxygen consumption (VO2)

Plasma brain naturetic peptide levels (BNP)

Endothelial function (RH-PAT)

9.2 Ethical Approval

The study was approved by the Tayside Committee for Medical Research Ethics (ref 05/S1402/46).

9.3 Introduction

Conventional dual chamber pacing maintains atrio-ventricular (AV) synchrony but may induce dyssynchronous activation of the ventricles, analogous to that associated with left bundle branch block {Leclercq, 1995 #943}. Therefore, any hemodynamic benefits of AV synchrony may be offset by right ventricular pacing induced ventricular dyssynchrony. This hypothesis is supported by results of a meta-analysis of randomized clinical trials comparing ventricular based with 'physiological' atrial based (mainly dual chamber) pacing, which found no difference in survival or heart failure, the only benefit of atrial based pacing being a reduction in atrial fibrillation, and a modest reduction in stroke{Healey, 2006 #144}. Pacing and implantable cardioverter defibrillator (ICD) trials show that adverse outcomes are associated with increased frequency of right ventricular pacing {Sweeney, 2003 #451}{Steinberg, 2005 #944}{Sharma, 2005 #945}and the degree of ventricular dyssynchrony induced {Shukla, 2005 #946}. Combining these findings, there is increasing evidence to suggest that conventional pacing, at the right ventricular apex, per se may be associated with adverse cardiovascular effects, even in the presence of preserved of AV synchrony.

The pathophysiological mechanisms underlying the adverse chronic effects of right ventricular pacing are not known and the aim of this study was to investigate the effects of right ventricular apical pacing on different cardiac physiological measures in subjects with dual chamber pacemakers for sino-atrial node dysfunction (SND). The cardiac physiological measures were chosen

to reflect vascular health, ventricular wall stress and cardiac reserve. Endothelial function, a powerful predictor of events in a variety of cardiovascular disease {Schachinger, 2000 #2284}{Yeboah, 2007 #2285}{Perticone, 2001 #2286}{Targonski, 2003 #2287}{Gokce, 2003 #2288} and a measure for vascular health was determined using reactive hyperemia peripheral arterial tonometry (RH-PAT), which is highly correlated with coronary endothelial function{Anderson, 1995 #16}. B-type Natriuretic Peptide (BNP) was determined to provide a measure of ventricular wall stress{Maeda, 1998 #948}. Cardiac output (CO) at rest and during exercise was determined non-invasively by an inert gas rebreathing method {Lang, 2009 #949}. The CO response to exercise provides a measure of cardiac reserve and is an important prognostic indicator in subjects with heart failure {Lang, 2009 #949}.

9.4 Methods

9.4.1 Recruitment

Patients were recruited from the Pacemaker Clinic at Ninewells Hospital.

9.4.2 Inclusion Criteria

Dual Chamber pacemaker in situ with a single ventricular lead located at the right ventricular apex.

Sinus Node Disease

9.4.3 **Exclusion Criteria**

Atrio-ventricular node disease.

Bundle Branch Block.

Heart failure symptoms.

Angina symptoms.

Age over 80 years.

9.4.4 Study Design

Subjects were seen at their initial visit, after informed consent and their pacemaker interrogated. This was a blinded crossover study with subjects assigned in a randomised order to 2 pacing interventions each lasting 7 days: dual chamber pacing with short AV delay time to produce maximal right ventricular pacing (RVP-max) and a control arm of minimal right ventricular pacing (RVP-min) using dual chamber pacing with long AV delay to allow intrinsic conduction to the ventricles. Prior to randomisation, as pre-study right ventricular pacing was variable among the subjects, pacing was programmed to produce minimal right ventricular pacing (using single chamber atrial pacing or dual chamber mode with long AV delay) for a minimal washout period of ≥1 week. Subjects were studied at baseline after washout, and after each 7-day pacing intervention with 7 days washout between the 2 pacing interventions. (See Figure 9.1). 7 days was selected as the period of intervention to allow haemodynamics to reach steady state.

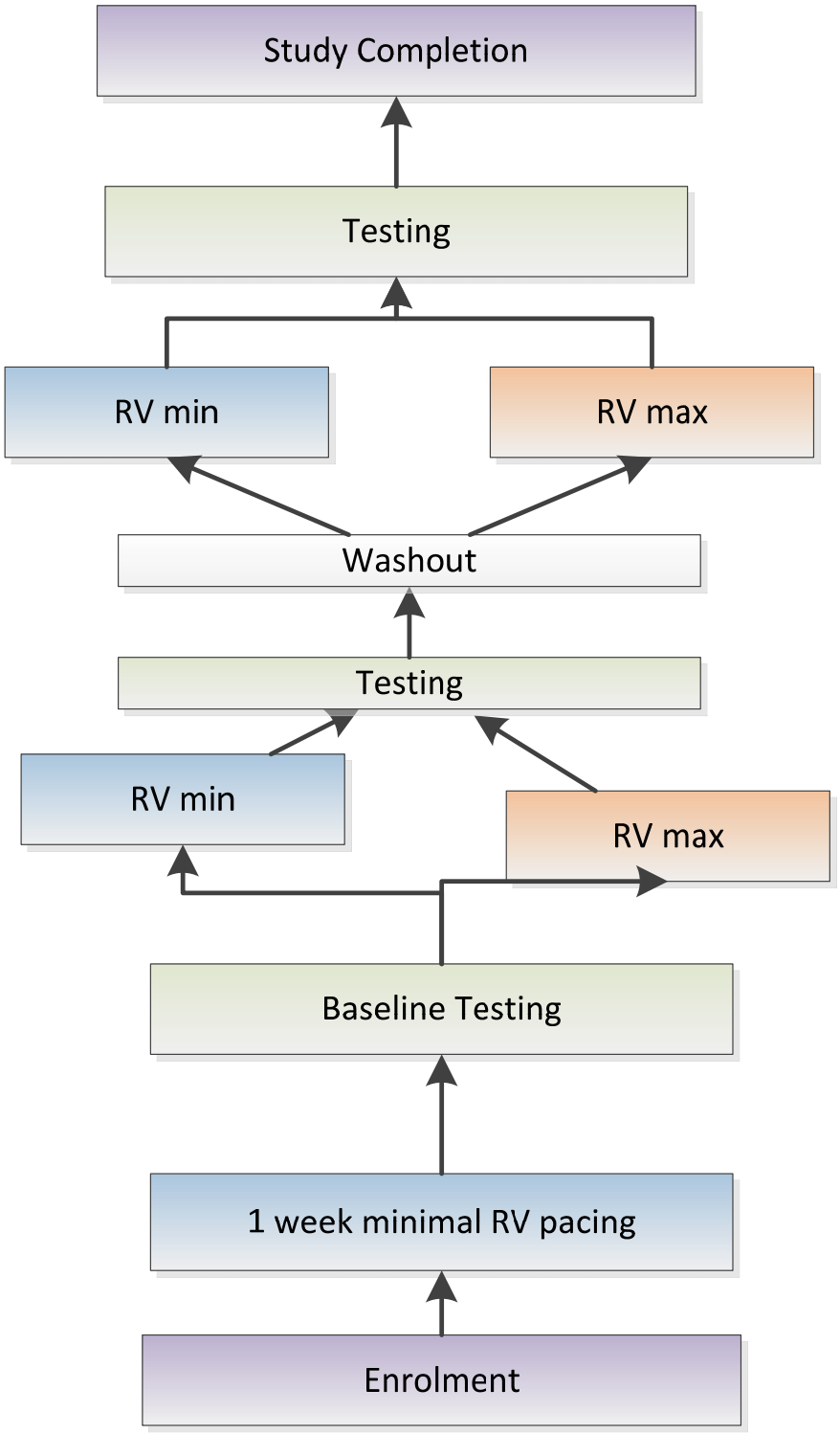


Figure 9.1 – Study Design

9.4.5 **Sample Size**

The power calculations, based on previous data {AlZadjali, 2009 #2611}, with a mean RH-PAT of 1.6 and standard deviation of 0.3 indicate that in order to have 80% power to detect a 20% change in RH-PAT in similar patients (alpha = 0.05), a sample size of 14 is required.

9.4.6 **Statistical Analysis**

All values are expressed as mean ± SD unless otherwise stated. Statistical analysis was performed with STATA SE11 (STATA Corp, Texas). Comparisons between RVP-max RVP-min were tested by paired t-test or by Fisher's exact probability test, as appropriate. A p value of 0.05 was considered statistically significant.

9.4.7 Clinical Measures

Peripheral endothelial function, cardiac output at rest and at peak exercise (rCO and exCO), and BNP were measured by a single investigator who was blinded to the pacing intervention. An independent un-blinded investigator performed interrogation and programming of the pacemakers at each study visit. The programmed base heart rate was increased by >5 b.p.m. over the intrinsic heart rate at randomisation and was constant in the two arms.

9.4.8 **Endothelial Function**

Endothelial Function testing was determined by reactive hyperaemia-peripheral arterial tonometry (RH-PAT) (Itamar Medical Ltd., Caesarea, Israel) (as described in the thesis introduction). The RH-PAT ratio ('RH-PAT Index') was defined as the ratio of the arterial pulse wave amplitude following a 5-minute arterial occlusion in the forearm to that of the pre-occlusion value. It has been has been validated against acetyl-choline mediated vaso-dilatation of coronary arteries, the gold standard in endothelial function testing (131, 149, 150) and RH-PAT highly correlates with coronary endothelial function, determined in this manner. Importantly, coronary endothelial function has been shown to be an important prognostic indicator (151). RH-PAT Index of <1.67 is considered to indicate a reduced reactive hyperaemic response in the peripheral vessels and therefore, endothelial dysfunction (152).

9.4.9 **Resting and Exercise Cardiac Output (CO)**

Cardiac output measures were obtained non-invasively using the inert gas rebreathing technique (Innocor, Innovision A/S, Odense, Denmark) (127). This method has been validated against the invasive gold standard where blood flow was measured from the pulmonary artery with a Swan-Ganz thermodilution catheter and it has been validated for use in many study populations (78, 127, 153). After 60 minutes of bed rest subjects breathed in N_2O (blood soluble gas) and SF_6 (blood insoluble gas) at concentrations of 0.5%

(V/V) and 0.1% (V/V) respectively through the Innocor re-breathing system. (as detailed in methods)

A standard exercise bicycle (Ergoline, Ergoselect 100P) protocol was used. Stages lasted 3 minutes starting with 0 watts; resistance was increased by 25 watts after each stage. Re-breathing tests were done at rest, 50 watts, and peak exercise. Subjects were asked to indicate a minute before terminating exercise to allow for the measurement of peak exCO.

9.4.10 **Plasma B-type natriuretic peptide (BNP)**

Venous blood samples were taken to measure BNP concentrations before exercise and after the subject had been supine for 60 minutes and were then aliquoted into appropriate tubes stored on ice. The samples were spun immediately at 3000 rpm for 10 minutes at 5°C in a Biofuge 28 RS centrifuge (Heraeus Instruments, UK). The BNP samples were stored at –70°C. BNP was extracted from plasma in C_{18} columns and then measured in a single batch by a blinded laboratory technician using radioimmunoassay (Bachem (UK) Ltd, St Helens, Merseyside UK).

9.5 Results

The clinical details of the 22 enrolled subjects are shown in Table 9.1. Subjects were mostly male and hypertensive.

Table 9.1 Baseline clinical characteristics.

Characteristic	
Number (% Male)	22 (77 %)
Age (years, ± SD)	67.7 ± 8.9
Time since device implant (years ± SD)	5.2 ± 4.5
Serum Creatinine (umol/L ± SD)	110 ± 66
Serum Haemoglobin (g/dL ± SD)	13.3 ± 1.4
Coronary artery disease	8 (36.4%)
Peripheral vascular disease	2 (9.1%)
Previous myocardial infarction	2 (9.1%)
Diabetes	5 (22.7%)
Hypertension	20 (90.9%)
Left ventricular ejection fraction <40%	5 (22.7%)
Left ventricular hypertrophy	10 (45.5%)
Medications	
ACE inhibitors	11 (50.0%)
Beta-adrenergic blockers	9 (40.9%)
Calcium channel blockers	6 (27.2%)
Diuretics	9 (40.9%)
Statins	15 (68.2%)
Nitrates	8 (36.4%)
Percentage of RVP (mean [SD])	8.8 ±14.7
Mean Heart rate ± SD	61 ± 4
Atrioventricular Delay (msec) ± SD	252 ± 54
Mean Systolic BP (mmHg) ± SD	144 ± 20
Mean Diastolic BP (mmHg) ± SD	78 ± 10

Mean RH-Pat Index ± SD	1.93 ± 0.43
Mean Resting Cardiac Output(L/min)	4.87 ± 1.36
Mean Exertional Cardiac Output (L/min)	8.05 ± 2.95

Measured variables in the 2 modes are shown in Table 2.

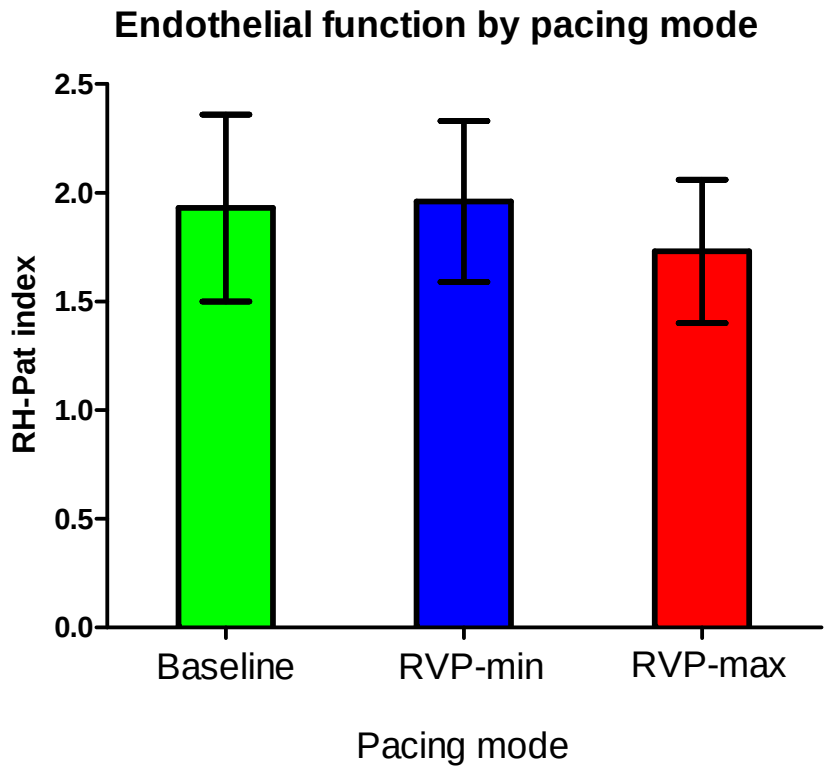
Table 9.2 Clinical measurements by pacing mode:

	RVP-min	RVP-max	P value
Percentage of RVP (mean ± SD)	14.7 ± 20.3	90.2 ± 15.7	< 0.05
Heart rate (b.p.m. mean ± SD)	64 ± 6	65 ± 7	NS
Atrioventricular delay (msec ± SD)	270 ± 43	113 ± 17	<0.05
Systolic blood pressure (mmHg, mean ± SD)	140 ± 18	140 ± 19	NS
Diastolic blood pressure (mmHg, mean ± SD)	76 ± 9	77 ± 10	NS
RH-PAT index (EnFI, mean ± SD)	1.96 ± 0.37	1.73 ± 0.33	<0.05
Resting cardiac output (L/min, mean ± SD)	4.75 (1.32)	4.27 (1.08)	NS
Exercise cardiac output (L/min, mean ± SD)	7.65 (3.15)	7.05 (2.61)	<0.05
B-type natriuretic peptide (ug/mL, mean ± SD)	104.3 (108.1)	112.8 (80.2)	NS

RVP-min=Dual chamber pacing with long AV delay; RVP-max= Dual chamber pacing with short AV delay; RH-PAT Index;

At baseline, after 'washout' with minimal RVP pacing at intrinsic heart rate, mean percentage right ventricular pacing was 8.8±14.7%. Right ventricular pacing was greatest in RVP-max mode (Table 9.2), as these subjects were almost constantly paced in the right ventricle in response to sensed and paced atrial beats. In contrast, mean percentage pacing during RVP-min pacing was lower, as sinus or paced atrial events were allowed to conduct to the ventricle via the intrinsic AV nodal pathway, and thereby inhibiting right ventricular pacing.

9.5.1 **Endothelial Function.**

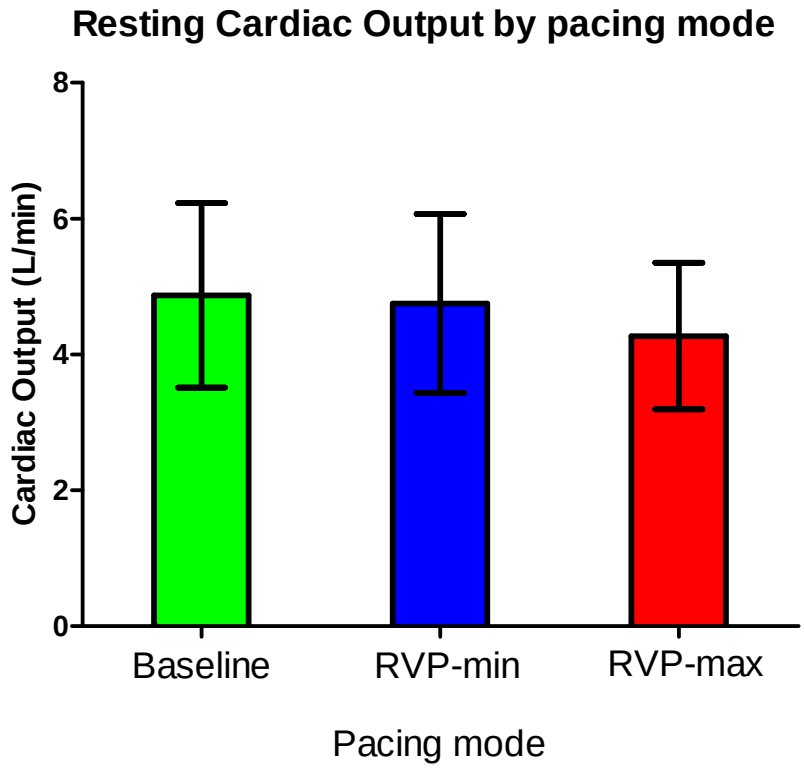


It was noted that the mean RH-PAT index was higher than may be expected at baseline for this cohort given 90% had hypertension. However it is important to

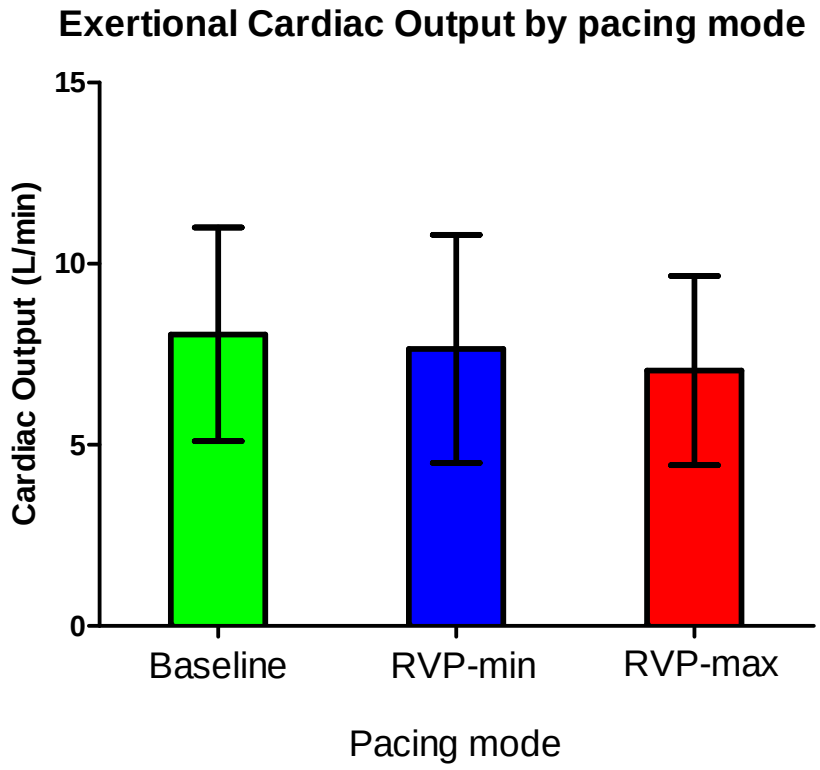
note that many were taking anti-hypertensive medication.

Endothelial function worsened in 15 subjects. RH-PAT was significantly lower in RVP-max mode compared to RVP-min (Table 9.2).

9.5.2 **Cardiac Output and Exercise Capacity.**



rCO tended to be lower with RVP-max when compared to RVP-min but the difference did not reach statistical significance (4.75 ± 1.32 versus 4.87 ± 1.36 p=NS). However, exCO during RVP-max was significantly lower compared to RVP-min (7.05 ± 2.61 versus 7.65 ± 3.15, $p<0.05$, Table 9.2).



9.5.3 **Plasma B-type Natriuretic Peptide.**

There was no significant difference in BNP between the 2 pacing arms (Table 9.2)

9.6 Discussion

As the development and adoption of biventricular pacing has become more widespread for patients with heart failure with impaired LV ejection fraction and left bundle branch block, (11, 12), there has been increasing understanding of the concepts of dyssynchrony and in particular *acquired dyssynchrony*

occurring as a result of right ventricular apical pacing. Many pacemaker trials have failed to show definitive superiority of dual-chamber compared to atrial based pacing for patients with sino-atrial node disease (7, 9, 10, 13) and it is likely that any potential benefits of assured atrio-ventricular conduction may be outweighed by the detrimental effects of activating the ventricles from the right ventricular apex. There has been much study into how to minimize right ventricular pacing for those who may not require it (13) and indeed there is evidence to support this approach both in terms of its efficacy (154) and importantly outcome(155). Whilst avoidance is possible in some patients with intermittent atrio-ventricular conduction problems it is clear in patients with complete failure of atrio-ventricular conduction this approach is not going to work.

Thus it is important that we focus on the pathophysiological mechanisms that may underpin the adverse outcomes seen with pacing the right ventricular apex. This study examined the effects of right ventricular apical pacing on different measures and is the first to demonstrate impaired endothelial function as well as a lower cardiac reserve associated with right ventricular apical pacing. This is important as both factors have been shown to determine outcome (127, 131)

High percentages of ventricular pacing, as seen in the RVP-max arm of this study, were associated with lower cardiac reserve and this may be due to acquired dyssynchrony.

Several studies have shown that activating the ventricles from the right

ventricular apex results in abnormal myocardial activation and dyssynchronous ventricular contraction, akin to dyssynchrony caused by left bundle branch block (24, 156). Previous studies also support this;

Lieberman and colleagues demonstrated that acute right ventricular pacing resulted in a reduction in cardiac output and stroke volume with impaired diastolic relaxation and increased left ventricular end-diastolic pressure in patients with and without impaired left ventricular function (157). This is consistent with the findings in this study - Cardiac output at peak exertion was significantly lower during maximal RV pacing compared to minimal RV pacing and indeed the cardiac output response to exercise has been shown to be prognostic (153).

In terms of patients with long term right ventricular pacing, Thambo et al examined 23 adult patients with complete congenital atrio-ventricular block who had ≥5 years of right ventricular apical dual-chambered pacing and found that prolonged ventricular dyssynchrony was associated with left ventricular remodeling, dilatation, asymmetrical hypertrophy, and overall lower exercise capacity than controls (59) .

Interestingly, Sadowski and Wozakowska-Kapłon compared plasma hormone levels in patients with atrial based versus dual chamber pacemakers and failed to show a difference in BNP levels (158), as was the case in this study

Endothelial function, assessed by RH-PAT Index was near normal (149) at baseline (1.93) which is perhaps surprising given the prevalence of

hypertension in the cohort, it is however, likely that they were well treated and use of ACE inhibitors and statins was high and these are known to improve endothelial function. Maximal RV pacing was associated with a fall in RH-PAT compared to minimal RV pacing. It is difficult to be certain regarding the exact mechanism for this, however, the RH_PAT measure has been validated against acetyl-choline mediated vaso-dilatation of coronary arteries, the gold standard in endothelial function. (131, 149, 150) and has been shown to be an important prognostic indicator(151).

Chronic right ventricular pacing has been shown to be associated with increased sympathetic activation (76, 77)as well as increased oxidative stress which is associated with reduced nitric oxide production (78) and up to 60 % of changes in RH-PAT may me mediated by changes in nitric oxide{Nohria, 2006 #4750}. Whilst these mechanisms may have a role in the effects of right ventricular apical pacing, in this study the interventions were relatively short (7 days) and so potentially the effects seen are mediated by changes in sympathetic activation. Potentially, acquired dyssynchrony may result in alternations in laminar flow which is known to occur in heart failure (159, 160) an coronary disease (161). This may result in decreased NO release and associated low and reciprocating shear stress may up-regulate pro-atherosclerotic genes and proteins that promote development of atherosclerosis (162, 163)

Endothelial function has been studied in paced subjects before. Fak et al studied the impact of VVI versus AAI pacing and noted an acute attenuation of

PMD associated with VVI pacing(164). Furthermore in a study by Rubaj et al (78) biventricular pacing was shown to reduce oxidative stress, NO metabolites and immune activation and was associated with enhance tissue perfusion in heart failure patients with pacemakers.

Measures of endothelial function have also been seen to predict response in patients with conventional indications for cardiac resynchronization therapy(79). The same group has also shown that implantation of a cardiac resynchronization device is associated with improvement in endothelial function.

9.7 Limitations

This study had several limitations. This was a small study but it was adequately powered to detect differences in endothelial function and CO. Although participants were fasted overnight, drank only water and not take any nitrate medication in the twelve hours prior to testing, their other vaso-active medications were only omitted in the morning of the test, this may have blunted the alterations in seen in endothelial function. No definitive conclusion can be drawn regarding the mechanisms between right ventricular pacing and endothelial function. Further studies are needed to elucidate these mechanisms. The potential benefits of alternative right ventricular lead location in patients indicated for brady-pacing is intensely being investigated {Curtis, 2007 #70}{de Teresa, 2007 #80}{Funck, 2006 #107}. Our study protocol did not

allow us to investigate the physiological effects of alternative right ventricular pacing sites such as pacing at the right ventricular outflow tract, septal pacing, and direct His bundle pacing. Nevertheless, our findings do support the general hypothesis that conventional right ventricular pacing with a high amount of right ventricular apical pacing has deleterious effects.

Endothelial function was assessed by only one measure. It is possible that the effects seen on the EndoPAT may not be demonstrated by other measures of endothelial function, not least as the mechanisms by which right ventricular apical pacing alters these measures in not fully understood.

The appreciation of the potential deleterious effects of right ventricular pacing and pacing induced dyssynchrony has led to large prospective mortality driven clinical trials(165-167)to compare biventricular pacing to conventional right ventricular pacing in subjects with brady-arrhythmia and without heart failure indications for biventricular pacing. Although these trials will determine mortality, they do not measure mechanisms that may underlie the outcomes of these trials. Although current pacemakers have algorithms to avoid unnecessary right ventricular pacing, 40% of pacemaker patients have AV node disease and require chronic ventricular pacing(81). Many questions remain as to the selection of the optimal pacing mode in subjects with and without structural or functional heart disease, or in young subjects with long term pacing requirements. A key to answering these concerns is an understanding of the pathophysiology of right ventricular pacing, such as the effect on endothelial dysfunction, which may be used as surrogate endpoints in the

evaluation of novel, and improved pacing modalities.

9.8 Conclusions

Right ventricular apical pacing is associated with worsened endothelial function and cardiac reserve and this should be evaluated in further studies.

10. CHOosing the rIght paCing mode in heart failure - The CHOICE study

10.1 Introduction

Patients with heart failure (HF) and left bundle branch block (LBBB) have reduced survival (168) compared to equivalent patients without LBBB. It is now recognized that LBBB results in abnormal ventricular activation and contraction (ventricular dyssynchrony) which can worsen cardiovascular function by reducing coronary perfusion and inducing mitral regurgitation, thereby reducing cardiac output. Recently, biventricular pacemakers (BVPs) which pace both ventricles simultaneously were developed to reverse the effects of LBBB and to 'resynchronise' ventricular contraction in severe HF ('Cardiac Resynchronisation Therapy', CRT). CRT in HF patients with LBBB has been shown to improve clinical and functional status, reverse adverse left ventricular remodelling, and reduce hospitalisation and death(11, 12, 105, 169-172). Therefore it is increasingly recognised that dyssynchrony is deleterious in HF and should be corrected if possible. This recent knowledge has wide implications because conventional pacemakers (CPs) with right ventricular (RV) pacing produces a LBBB pattern which can lead to ventricular dyssynchrony. Indeed, RV pacing has been associated with increased mortality and morbidity in severe CHF(7, 173). The MOST study (3) demonstrated that for every 10% increase in cumulative time spent in RV pacing, subjects had a corresponding 20% increased risk in HF hospitalisations. Similarly, the DAVID trial(7) showed that in patients with implantable defibrillators (ICDs), unnecessary RV pacing was associated with increased mortality and heart failure hospitalisations. The

current evidence suggests that the non-physiologic nature of RV pacing may cause structural and electrophysiological remodelling, predisposing to the development of heart failure and atrial fibrillation(36, 174).

Currently, BVPs are only used to improve heart failure symptoms in HF patients with LBBB, and are not routinely implanted to treat bradycardia(175). In practice, these patients would receive a conventional pacemaker. However, a few observational studies in patients with existing conventional pacemakers and severe HF(107, 176-178), have shown that upgrading to biventricular pacing results in improved quality of life scores, left ventricular ejection fraction, exercise capacity and NYHA class within 3 months of upgrade.

At present, there is little data to support specific guidelines(177, 178) regarding the type of pacemaker to use at initial implant for HF patients who need pacing for symptomatic bradycardia and high grade atrioventricular block, in particular patients with mild to moderate HF. Currently, in clinical practice it is difficult to predict in HF patients if or when conventional pacing will worsen HF, and whether these patients would benefit from biventricular pacing instead at the initial implant. The advantage of initial BVP implant is that HF deterioration due to RV pacing induced dyssynchrony may be avoided. The alternative approach would be to use a CP initially and upgrade to BVP those patients who worsen with conventional pacing. However, this approach not only subjects patients to increased risk and discomfort, but also may not be cost effective because of the high device and procedure cost for each implant. Arguably therefore, HF patients presenting with bradycardia indications for pacing, should receive

BVPs in the first instance, in order to avoid acquired LBBB and ventricular dyssynchrony from conventional pacing. In a recent abstract (179), these patients constituted at least 20% of all pacemaker referrals, and that 80% of these patients will have significant RV pacing after implant.

Two major trials of pacing mode undertaken in patients who require pacing for bradycardia who have impaired left ventricular systolic function have recently reported and demonstrated improved symptoms and outcomes where these patients receive biventricular pacing{Curtis, 2013 #4743}{Stockburger, 2011 #4746}. These studies did not, however, examine the mechanisms which may determine the outcome.

This study therefore aims to assess functional response and elucidate the mechanisms underlying these functional changes, helping to define the mechanisms whereby RV pacing may be harmful, or that biventricular pacing may be beneficial. Improved exercise capacity can result from improvement in parameters of cardiac performance (cardiac output) as well as peripheral oxygen extraction which is dependent on skeletal muscle oxygen extraction and oxygen delivery (via blood vessels). This study aims to measure the effect of pacing on cardiac output on rest and exercise. In this regard, we have the ability to measure (using the Innocor System (Innocor, Innovision A/S, Odense, Denmark) simultaneous cardiac output and peak oxygen consumption. It is a reliable, safe, and inexpensive method for non-invasive measurement of cardiac output and it has been validated in both healthy subjects and patients

with CHF(128, 180). In addition to cardiac output, we will also obtain measurements of echo derived myocardial systolic and diastolic function. Improvement in endothelial function leading to better muscle perfusion can lead to improved exercise capacity. Indeed, in the study by Regensteiner et al of diabetic patients who were treated with rosiglitazone, the improvement in exercise capacity was related to an improvement in endothelial function (134). Therefore, this study will also examine the effect of pacing on endothelial function, a surrogate marker of the disease process in CHF.

10.2 Objectives

10.2.1 Study Aim

The aim of this study was to assess whether patients, with an indication for a conventional pacemaker, who receive a biventricular pacemaker have greater exercise capacity as measured by the 6 minute walk test.

10.2.2 Secondary Aims

The secondary aims of this study were to determine whether biventricular pacing improves the cardiac output in patients with bradycardia and stable heart failure and to determine whether biventricular pacing results in less endothelial dysfunction and other markers of cardiac vascular stress.

10.3 Methods

10.3.1 Ethical Approval

The study was approved by the Tayside Committee for Medical Research Ethics (ref 09/S1401/45)

10.3.2 Study Population & Recruitment

Subjects were recruited from the permanent pacemaker waiting list within Ninewells Hospital. Individuals were initially provided with an information sheet outlining the study, and their permission obtained to discuss participation at least 24 hours subsequently. Informed consent was then obtained to screen for inclusion in the study.

After consent has been obtained and inclusion and exclusion criteria (below) confirmed, I implanted a biventricular pacemaker. In 1 patient I was unavailable and the device was implanted by Dr. Choy and Dr. Affolter.

Study Inclusion Criteria

Left ventricular systolic dysfunction (EF < 40% by echocardiography)

Atrio-ventricular node disease.

Anticipated to be more than 40% paced in the ventricle

Study Exclusion Criteria

Patients unable to cope with a breathing mouthpiece and stationary cycling.

Patients meeting criteria for CRT by current guidelines (i.e. NYHA class lll-lV, optimal medical therapy, QRS>120ms)

Recent (within 1 year) hospital admission for heart failure.

Life expectancy less than 12 months.

Inability to walk independently.

10.3.3 Study Design

This was a randomised double blind cross-over study. (Figure 10.1)

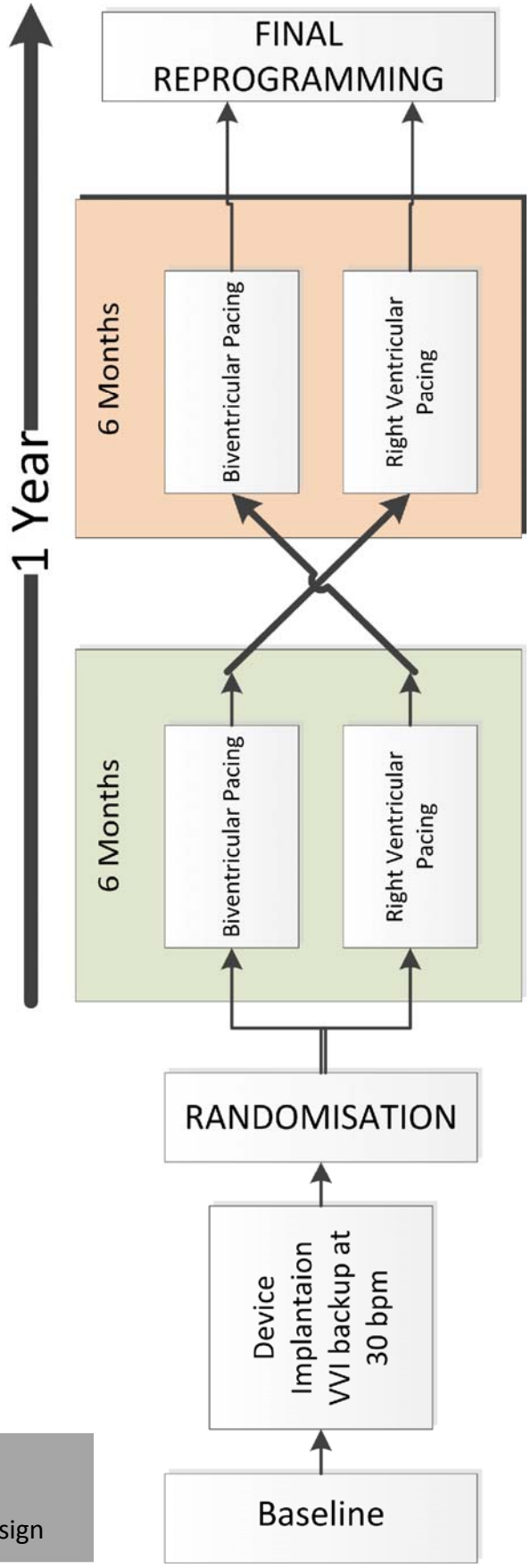


Figure 10.1

CHOICE Study Design

10.3.4 Clinical Measures

The following clinical measurements were performed as described in Methods Chapter 2.

- 6 Minute Hall Walk Test
- Non-invasive blood pressure measurement.
- Endothelial Function Testing using EndoPAT
- Non-invasive cardiac output measurement using standard exercise protocol.
- Patient Questionnaires – EuroQol and Minnesota living with heart failure.
- Venepuncture and hormone assay for the following:
    - B-naturietic peptide
    - hsCRP

10.3.5 Statistical Analysis

All statistical analyses were performed using SPSS version 21 (IBM Corp).

In order to account for any potential interaction occurring as a result of the order by which the subjects received each pacing mode, a mixed model linear regression analysis was employed to determine, and adjust for, the presence of any such interaction and the baseline values for each measure.

The study arm and the period during which this was recorded were entered as centred co-variants, encoded as -0.5 and +0.5. A further interaction term was included as the product of the two and all were entered into the model as fixed effects together with baseline data.

10.3.6 Reporting Results

Results are presented as mean ± standard deviation for normally distributed data and geometric mean ± 95% confidence intervals for non-normally distributed data.

A p value of 0.05 was considered statistically significant.

10.3.7 Power and Study Sample Size

The primary endpoint in the study was difference in 6 minute hall walk distance after 6 months of conventional versus 6 months of biventricular pacing. Based

upon previous data, the study was powered to detect a change in walking distance of 30m.

The relationship between patients' global rating of change in condition and 6 minute walking distance indicates that a 30 metre improvement is of importance (133), further supporting the selection of this magnitude of change in primary outcome. Based on previous study data investigating biventricular pacemaker insertion in heart failure patients, to detect a 30m change in 6MW distance in a crossover sample with a power of 80% at the $p<0.05$ level, 25 patients are required.

For the secondary endpoints of endothelial dysfunction, based on the results of the previous data (181), to detect a 10% change at 80% power at $P<0.05\%$, the sample size required is 31.

To allow for subject dropout I therefore aimed to recruit 40 subjects.

10.4 Results

10.4.1 Population

24 patients agreed to be screened for the study and undertook informed consent. Left ventricular lead placement was not technically possible in 1 patient, who received a conventional right ventricular pacemaker and exited the study. 1 patient died prior to randomisation. 22 patients were randomised. 3 patients died during follow-up, two in one arm(right ventricular pacing) and one in the other (biventricular pacing). The causes of death were progressively worsening heart failure and cerebrovascular accident.

Worsening heart failure was a pre-determined adverse event requiring study exit. The only patient who exited the study with worsening heart failure did so after a switch from the biventricular pacing arm to the right ventricular pacing arm.

Recruitment failed to meet targets. Despite my original work to determine the population and ensure the recruitment was feasible I was unable to recruit the target population. Recruitment had to close when I left my research post as my employment moved to another city and I was unavailable for implants or follow-up.Data from patients who died were excluded from follow-up.

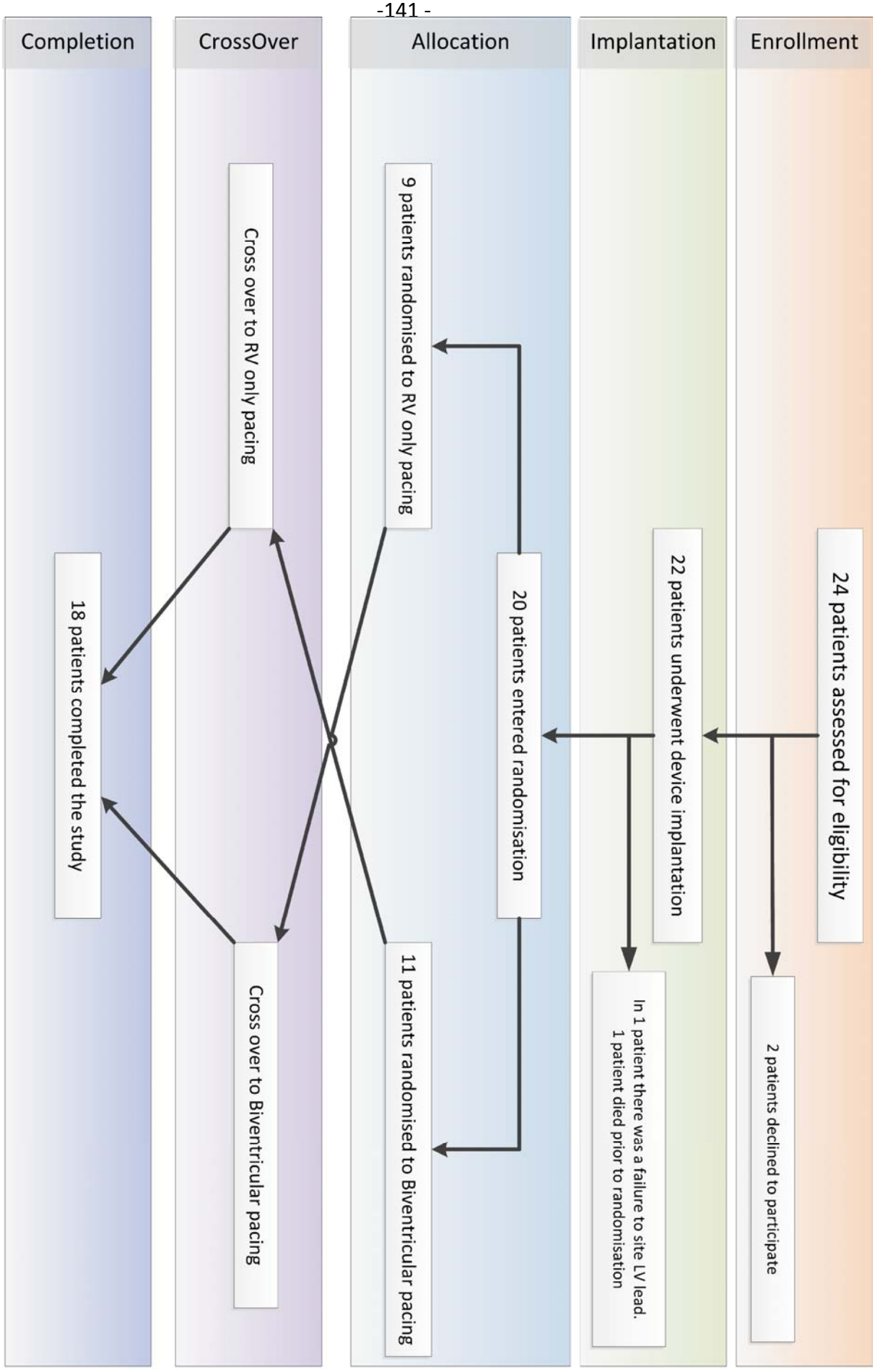


Figure 10.2 – CHOICE study design

Table 10.1 – Baseline Characteristics

Characteristic	Value
Number (% Male)	18 (89%)
Age (years)	74.4 ± 7.4
Height (metres)	1.69 ± 0.09
Weight (kilograms)	81 ± 13
Estimated GFR (mls/min/1.73m^2)	52 ± 11
Haemoglobin (g/dl)	13.7 ± 2
Coronary artery disease (%)	11 (62%)
Diabetes (%)	2 (11%)
Left ventricular ejection fraction <40% (%)	18 (100 %)
Atrial Fibrillation (%)	6 (33 %)
Medications	
ACE inhibitors	17 (94%)
Beta-adrenergic blockers	13 (72%)
Diuretics	17 (94%)
Statins	11 (61%)
Heart rate (bpm)	63.5 ± 17.8
QRS duration (ms)	115 ± 17
Systolic BP (mmHg)	132 ± 19
Diastolic BP (mmHg)	76 ± 11
6 minute hall walk test (metres)	330 ± 118
RH-Pat Index	1.73 ± 0.49
Total Exercise Time (minutes)	5.54 ± 2.76
Peak Oxygen Consumption (L/min)	0.886 ± 0.49
Resting Cardiac Output(L/min)	2.59 ± 1.21
Peak Exertion Cardiac Output (L/min)	4.95 ± 1.94

10.4.2 6 minute hall walk test

The total distance covered in the 6 minute hall walk test was significantly higher (347 ± 123m v 390±128m, p = 0.04) in the biventricular paced arm of the study, as was the change in distance compared to baseline which was +36 ± 93m in the biventricular group, and –6 ±115m in the right ventricular group (P = 0.04)

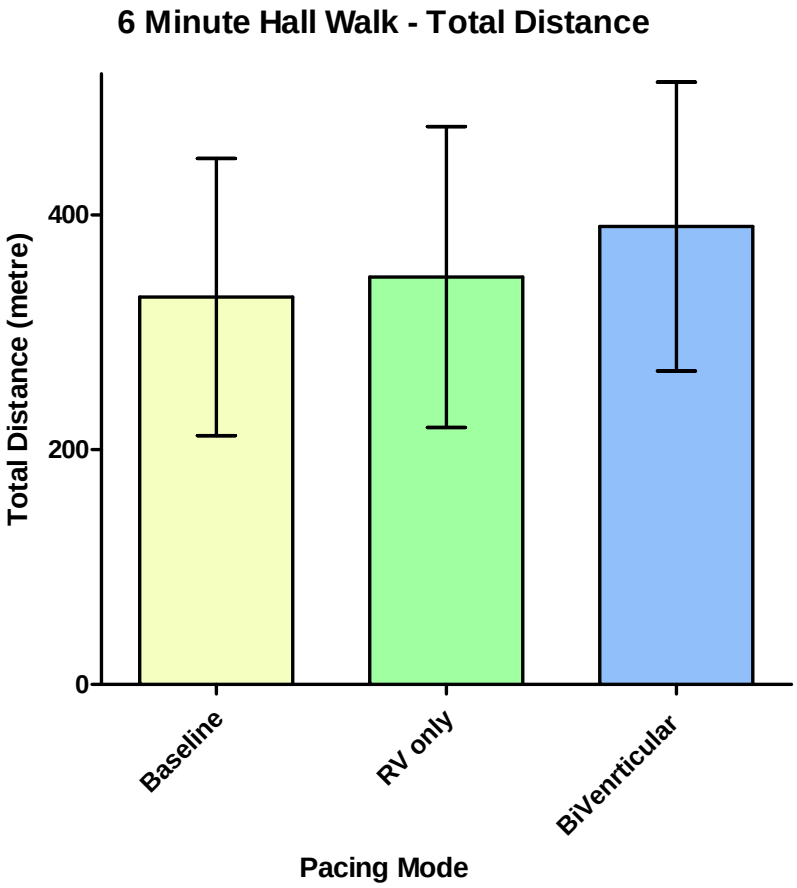


Figure 10.3 – 6 minute hall walk distance by pacing mode

10.4.3 Endothelial Function Testing

In 2 subjects, at separate sittings, reliable RH-PAT measurements could not be obtained, and as these patients thus had incomplete data they were excluded from the analysis. In the remaining 16 patients, there was a significant difference in the RH-PAT index between the study arms. The mean RH-PAT index during right ventricular pacing was 1.5 and during biventricular pacing it was significantly higher at 1.75 (p=0.05)

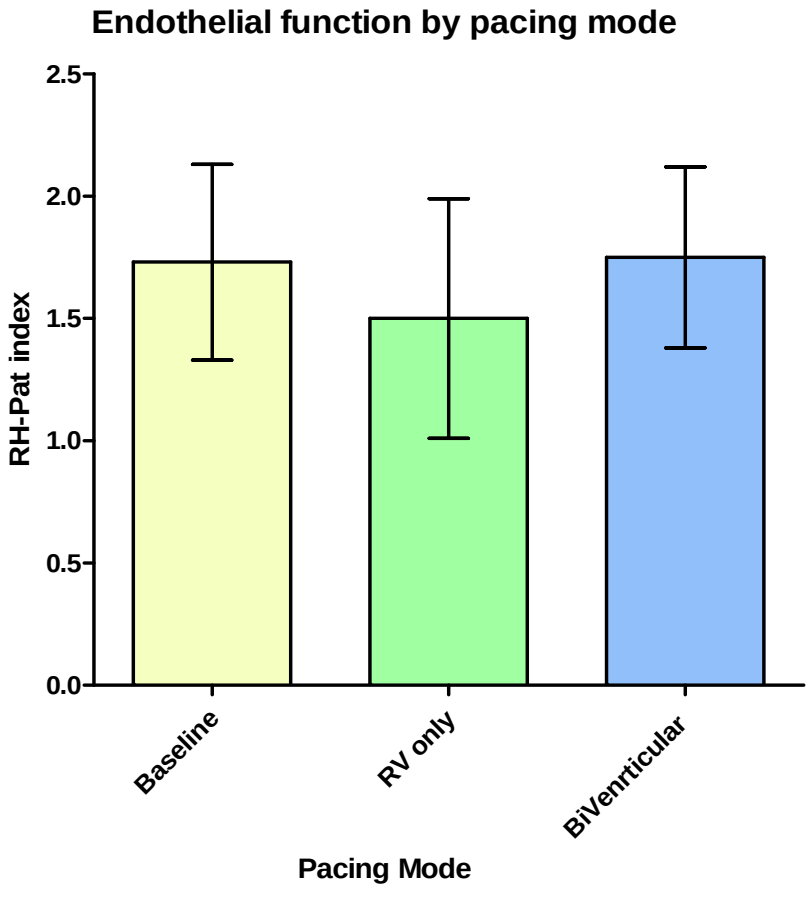


Figure 10.3 – Endothelial function by pacing mode

10.4.4 Blood Marker Levels

There was no significant difference in the levels of BNP observed at the end of each treatment arm, the values for biventricular pacing and right ventricular pacing were 47 [IQR 16 – 82] pg/ml and 31 [IQR 17 – 53] pg/ml respectively (p=0.091).

High sensitivity c-reactive protein levels were, however, significantly lower in the biventricular arm, 2.8mg/ml v 9.7 mg/ml (p=0.02).

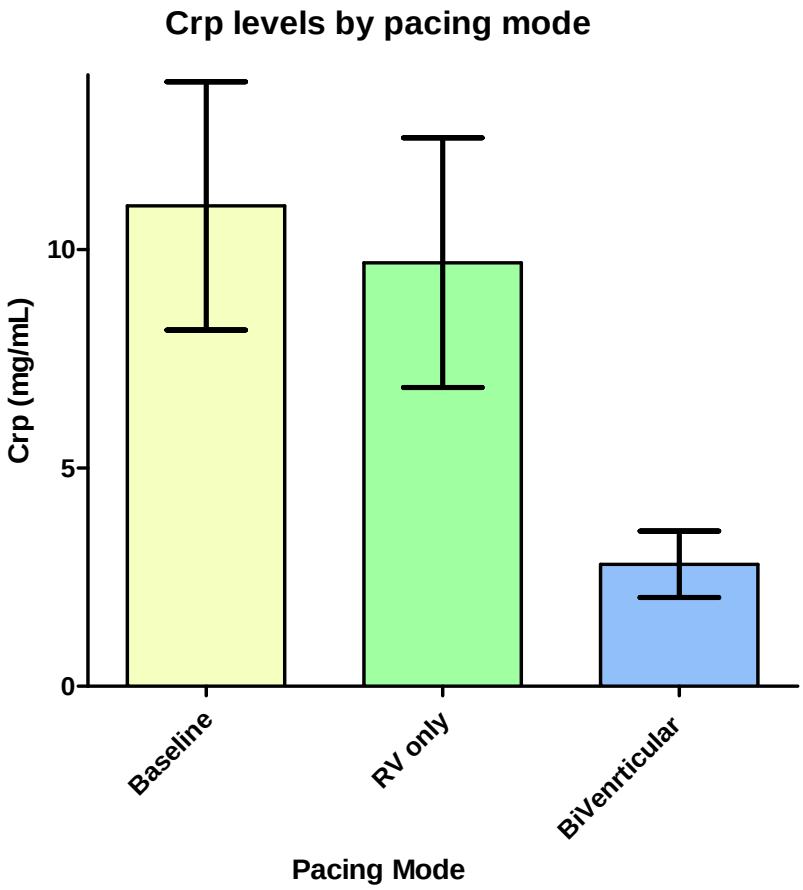


Figure 10.4 – Crp by pacing mode

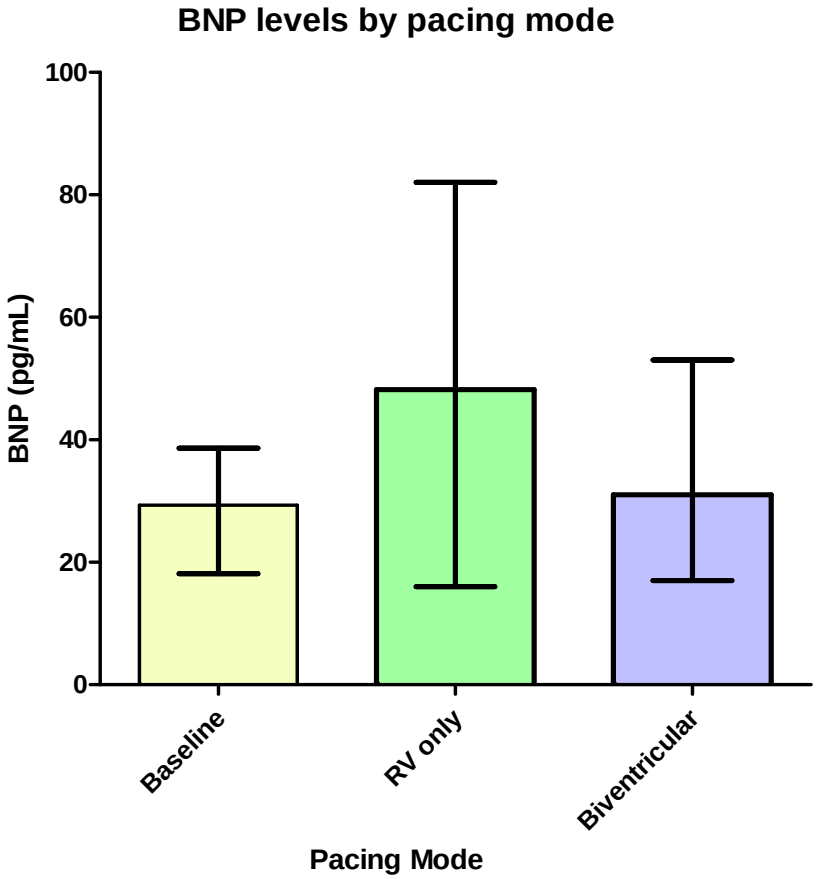


Figure 10.5 – BNP by pacing mode

Table 10.2 – Measurements at the end of each study period.

Measure	Baseline (BL)	RV only pacing (RV)	Bi-ventricular Pacing (Biv)	P (BiV v RV)
BNP	31.2 [18.1 – 38.6]	46.5 [16 – 82]	31 [17 – 53]	0.09
CRP	11	9.7	2.795	0.029
6 minute hall walk test				
Total distance (m)	354 ± 104	347 ± 123	390 ± 128	0.037
Endothelial Function				
RH-PAT index	1.73	1.5	1.75	0.05
Cardio-Pulmonary Exercise Testing				
Resting CO	2.60 ± 1.95	2.28 ± 0.59	2.37 ± 1.13	0.54
Peak CO	4.99 ±2.00	4.37 ± 2.68	5.31 ± 2.68	0.085
Resting V02	0.264 ± 0.16	0.286 ± 0.08	0.257 0.11	0.104
Peak V02	0.885± 0.49	0.869 ± 0.57	0.879 ± 0.61	0.905
Exercise Time	5.75 ± 4.23	5.97 ± 4.2	6.69 ±4.12	0.311
Echo Parameters				
Ejection Fraction	27 ± 9.30	37.5 ± 13.6	43 ± 9.51	0.01
LVIDD	5.98 ± 0.90	5.61 ± 2.2	5.58 ± 1.1	0.792
LVIDS	4.82 ± 1	4.35 ± 2.2	4.42 ± 1.1	0.934
LV pre-ejection time	29.1 ± 10.6	30.98 ± 23.2	28.3 ± 1.3	0.652
RV pre-ejection time	13.8 ± 5.6	15.3 ± 10.8	15.4 ± 4.45	0.112
Patient Questionnaires				
MLWHF	31 ± 20	17 ± 16	15 ± 16	0.645
EQ-5D - VAS	64 ± 12	66 ± 25	75 ± 17	0.06

10.5 Discussion

Whilst there have now been several studies exploring the benefits of biventricular pacing in patients who require bradycardia support, both with and without impaired left ventricular systolic function(107, 109) this study sought to explore the impact of biventricular pacing on the previously demonstrated detrimental effects observed from right ventricular pacing on endothelial function.

The HOBIPACE study undertaken by Kindermann et al (107) also investigated the impact of biventricular pacemaker insertion for patients with heart failure and bradycardia. There are some important differences between HOBIPACE and this study. Firstly the entry criteria for HOBIPACE included LVIDD of greater than 6 cms, thus restricting including a sub-set of patients with dilated ventricles, and the population had a mean NYHA functional class of 3 at baseline, with the majority having left bundle branch block (63%) with a mean intrinsic, un-paced QRS duration of 174 ms, essentially meeting conventional indications for biventricular pacemaker implantation irrespective of their bradycardia. Secondly the study included a mix of patients receiving de novo implants as well as those undergoing siting of a left ventricular lead to upgrade, thus some patients will have already been exposed to right ventricular pacing for some time. Thirdly all patients were exposed to a “run in” phase of biventricular pacing, which may have afforded some pre-conditioning and fourthly there was a mix of right ventricular pacing sites with 43% paced at the

apex and 57% paced from the right ventricular septum, although current evidence suggests both sites of RV lead placement are associated with similar outcome(182, 183). Yu et all enrolled 177 patients with bradycardia and normal left ventricular ejection fraction to a double blind randomised crossover study of biventricular versus right ventricular apical pacing. Yu was also able to demonstrate the superiority of biventricular pacing in this study. Right ventricular pacing was associated with a significant reduction in left ventricular ejection fraction and left ventricular systolic volume.

10.5.1 Study Population

It is important to highlight that the population enrolled in the study were well treated in respect of heart failure medication (94% were receiving an ACE inhibitor or angiotensin receptor blocker and 94% were receiving diuretic therapy) and were clinically stable at enrolment. They did not meet conventional indications for cardiac resynchronisation implantation as evidenced by a mean QRS duration of 115 milliseconds.

There were 2 deaths during the study period, which reflects the perilous nature of heart failure and in particular that of heart failure and bradycardia. As one might expect the population were elderly, however they were active at baseline with a mean 6 minute hall walk distance of 330 metres.

10.5.2 Exercise Capacity

Consistent with previous studies this study demonstrates the superiority of biventricular pacing in the 6 minute hall walk distance. As previously described the 6 minute hall walk is an important measure which has been shown to reliably reflect exercise tolerance and capacity in elderly patients with heart failure(184).

In this study biventricular pacing was shown to be superior to baseline and right ventricular pacing in terms of 6MWT, whilst right ventricular pacing alone was unchanged compared to baseline.

The difference in total exercise time during cardio-pulmonary exercising failed to be statistically significant between the two arms. ($p = 0.311$.)

Right ventricular pacing was associated with a heightened inflammatory state as evidenced by the trend to higher BNP and cRP levels and the significantly lower RH-PAT index, suggesting reduced endothelial reactivity. Importantly there was no significant difference between RH-PAT index between baseline and the end of the biventricular phase, rather right ventricular pacing was associated with significant reduction in endothelial reactivity, as demonstrated in the previous study (181). This finding suggests that whilst biventricular pacing had little impact from baseline, it did appear to protect from the potentially detrimental effects of right ventricular pacing.

10.5.3 What are the potential mechanisms by which pacing site affects the endothelium

The potential hypotheses by which right ventricular pacing maybe associated with reduced endothelial reactivity have already been discussed. In particular, speculating that dyssynchronous pacing may cause loss of laminar spiral flow, previously shown to occur in coronary artery disease (161) and heart failure (159, 160). A previous study has demonstrated changes in flow characteristics in the internal and external carotid arteries after right ventricular pacemaker implantation (185), which may give credence to the hypothesis.

The endothelium itself has been shown to react differently when exposed to laminar and non-laminar flow stress with the former promoting up regulation of “vasoprotective” genes within the endothelium itself (186). Whilst the non-laminar stress appears not to result in such expected up regulation, and may even lead to reduced endothelium derived nitric oxide synthesis. (162)

Furthermore biventricular pacing has been shown to reduce ventricular dyssynchrony and thus may be expected to promote laminar flow. Indeed, Rubaj et al (78) investigated the effects on immune and endothelial activation in 28 heart failure patients with biventricular pacing. After 1 week of right ventricular only pacing, the study reported significant elevation of N-terminal pro-Brain natriuretic peptide and reduction in nitric oxide metabolites. Indeed the authors conclude that the effects of biventricular pacing extend “beyond improving cardiac haemodynamics”. Additionally Fak et al demonstrated a reduction in flow mediated dilation in 12 patients with dual chamber

pacemakers when they were exposed to ventricular demand pacing compared to atrial based pacing.

Akar et el (187) examined predictors of response to cardiac resynchronisation therapy. Whilst subjects met accepted biventricular implant criteria (QRS > 120ms, left ventricular systolic impairment) and did not require bradycardia support per se, Akar and colleagues observed a correlation between impaired flow mediated dilatation and likely response to biventricular pacemaker insertion ($r = 0.39$, $P = .03$). Furthermore the authors report that this predictive value was noted to be independent of other measures including QRS duration, left ventricular ejection fraction, or measures of dyssynchrony suggesting that endothelial function may be a further measure by which clinicians may identify responders to biventricular pacing in a heart failure population.

10.5.4 Cardio-pulmonary exercise testing

In this study there was no significant difference between the biventricular and right ventricular pacing arms. It should be noted that the study was not powered to detect such a difference. Previous studies with larger populations (107, 109) have demonstrated significant improvement in exercise time and peak oxygen consumption and cardiac output in the biventricular pacing mode. Importantly we did not observe worsening of cardiopulmonary exercise test measurements associated with biventricular pacing.

10.5.5 Patient perception

In managing a chronic long term condition such as heart failure, patient perception and morbidity are vitally important measures.

I observed no significant difference in the MLWHF score between pacing modes, however the was a trend (p=0.06) to enhanced quality of life in the EQ-5D visual analogue scale in biventricular compared to right ventricular pacing (66 v 75). To out this into context the mean change seen in a recent study of a cohort of patients undergoing knee replacement surgery was 3.3{Lin, 2013 #4752}.

The data suggests that patients may have a better overall sense of wellbeing when receiving biventricular pacing, whilst the improvement may not be sufficient to change the response to the structured question on the MLWHF questionnaire. The later may have been the result of exclusion of patients with significant heart failure, who met CRT indications directly and thus were not eligible for study entry. Similarly 6 months of right ventricular pacing may be too short a period to result in significant change.

10.6 Limitations

The main limitation of this study was the failure to recruit the target number of participants and the mortality during study follow-up. The latter highlights the

perilous nature of heart failure, and the former highlights the real-world prevalence of this population may be less than originally anticipated. This has likely resulted in the study being underpowered to detect differences in cardio-pulmonary exercise testing and other measures.

Many current device implanters would favour implantation of the right ventricular lead upon the right ventricular septum when implanting univentricular pacing system and select the apex for a biventricular system to promote resynchronisation. This means that it may be difficult to extrapolate the results of this study to modern practice where right ventricular septal lead implantation may ameliorate some of the deleterious effects of right ventricular pacing as discussed in the introduction of this thesis, {Khan, 2011 #4734}(183) although there is no definitive pool of evidence in this regard.

The study used only 1 measure of endothelial function – EndoPAT. Whilst, as previously discussed, this measure has been validated against coronary acetyl choline mediated flow dilatation in normal subjects and patients with diabetes and cardiac failure, as the mechanisms by which pacing may alter endothelial function and not fully understood, it is possible that an unknown interaction explains the measured effects in this study. It should be noted, however that other studies have described a reduction in FMD associated with right ventricular apical pacing.

10.7 Conclusions

Biventricular stimulation is superior to right ventricular apical stimulation in patients with impaired left ventricular systolic function and atrio-ventricular block. Biventricular pacing is associated with improved quality of life and increased exercise capacity in such patients.

11. The observed effects of Renin-Angiotensin System Blockers in patients paced for complete Atrio-Ventricular Block.

Paper published as :

Renin-Angiotensin System Blockers are Associated with Reduced Mortality and Heart Failure Hospitalisation in Patients Paced for Complete Atrio-Ventricular Block

Heart Rhythm. 2012 Apr;9(4):505-10. Epub 2011 Nov 15

11.1 Introduction

Cardiac pacing is the mainstay of treatment for symptomatic bradyarrhythmias, and improves morbidity and mortality in patients with significant sinus and atrio-ventricular node disease. However, pacing from the right ventricular apex can induce dyssynchronous activation of the ventricles, increase sympathetic activation (76, 77) cause abnormalities in myocardial perfusion(188), reduce endothelial function, cardiac output(181), and left ventricular ejection function; and cause adverse cardiac remodelling(109), and may result in pacing induced heart disease that is associated with adverse cardiovascular effects(141). Increased frequency right ventricular pacing (3, 7-9) and the degree of ventricular dyssynchrony induced (10) has been shown to be associated with worse cardiovascular outcomes. It appears that right ventricular pacing per se is harmful, since trials comparing atrial based pacing with a dual chamber device, have failed to demonstrate benefit in terms of survival or heart failure(36, 189-191) compared to ventricular based pacing, whilst the Danish study (39), utilizing single chamber atrial pacing only, found beneficial cardiovascular effects and a reduction in mortality. This appreciation of the potential deleterious effects of right ventricular pacing and pacing-induced dyssynchrony has led to pacing algorithms to avoid unnecessary right ventricular pacing(41). However, given 40% of pacemaker patients have AV node disease and require chronic ventricular pacing(81), other strategies need to be explored. Whilst prophylactic biventricular pacing has been

proposed(192) and is being tested in a large on-going study(167), pharmacological strategies also need to be considered. Right ventricular pacing leads to ventricular dyssynchrony which is strongly influenced by haemodynamic change such as afterload(110) and left ventricular fibrosis (111). In a recent study involving a dog pacing model, Kurita and colleagues showed that blockade of the renin-angiotensin system (RAS) with an angiotensin converting enzyme inhibitor (ACE-I) diminished left ventricular dyssynchrony through ACE-I induced reduction in afterload and left ventricular wall stress and reduction in myocardial fibrosis(117). However, the impact of ACEI therapy on survival in patients with pacing induced heart disease is not known. We hypothesize that RAS blockers (RASB) such as with ACEI or angiotensin receptor blockade (ARB) use may be beneficial in counteracting any potentially harmful effects of right ventricular pacing. To test this hypothesis we examined, retrospectively, the impact of these therapies on survival and heart failure hospitalisation in patients with right ventricular pacemakers implanted for complete atrio-ventricular (AV) block, and thus most at risk of pacing induced dyssynchrony resulting from a high degree of right ventricular pacing.

11.2 Study Aim

The aim of this study was to explore the impact of renin-angiotensin blocking agents in patients with right ventricular pacemakers.

Specifically this study aims to determine whether patients receiving renin-angiotensin blocking agents were protected from heart failure admission or death compared to those who naïve to these agents.

11.3 Ethical Approval

The study was approved by the Tayside Committee for Medical Research Ethics (ref 05/S1402/46).

The study was approved by the Tayside Caldicott Guardian.

This data used in this study was approved for release by the Tayside Cardiology IT sub-group.

11.4 Methods

11.4.1 Study Population

Permanent pacemaker in situ with a single ventricular pacing electrode located at the right ventricular apex.

Complete Atrio-ventricular block.

11.4.2 Study Design

This was a retrospective observational study.

Data from multiple datasets was deterministically linked at the level of the individual by means of community health index number, as previously discussed.

The datasets used in this study, which have been discussed and detailed previously include:

- Tayside Pacing Registry
- Scottish Morbidity Record
- General Registry Office – Death Certification
- Tayside Dispensed Prescription data

Access to the resulting anonymised research dataset was administered by the Health Informatics Centre at the University of Dundee using protocols approved by the East of Scotland Research Ethics Committee.

11.4.3 Statistical Analysis

Statistical analysis was performed with STATA SE11 (STATA Corp, Texas).

Categorical data were analysed by the chi-square test and continuous variables by t-test or the non-parametric Mann-Whitney U test as appropriate. Results are presented as mean ± standard deviation for normally distributed data and geometric mean ± 95% confidence intervals for non-normally distributed data.

Compliance with RASB therapy was determined by calculating the mean of the intended duration of therapy for each prescription expressed over the interval of days until the next prescription was issued. If subsequent prescriptions were issued before the end of a previous prescription censoring of the previous prescription occurred, thus maximum possible adherence was 100%.

The effects of known prognostic variables upon outcome were studied using a Cox proportional hazards regression model with age at implant, sex, social

deprivation score, presence or absence of prescription of cardiovascular drugs after implant, diabetes, prior history of myocardial infarction, prior history of heart failure, presence of atrial fibrillation and serum creatinine expressed as a mean throughout the study period.

We also performed several sensitivity analyses, recognising that patients often stop and start treatment throughout their lives, and that, any analysis of impact of drug therapy may be subject to potential immortality bias(126). To account for this we performed a time-dependent analysis with a time dependent variable to express the status of RASB use throughout the study period. Secondly, a propensity score (a conditional probability of exposure to a treatment given observed co-variants) was determined using a logistic regression model. We utilized this score to perform a subgroup analysis in which cohorts of RASB exposed and unexposed subjects were matched for propensity score. Schofield residuals were assessed to ensure that the assumptions for cox's proportional hazards model were met.

All statistical analyses were performed using Stata (SE) version 11.1 (Stata Corp Texas). A p value of 0.05 was considered statistically significant.

11.4.4 Censoring

Patients were censored when they left the region.

11.4.5 Outcome

11.4.5.1 All-cause Mortality

The primary outcome for this study was all-cause mortality. Mortality was defined as any entry in the General Registry Office dataset confirming mortality.

11.4.5.2 Heart Failure Hospitalisation

Heart failure hospitalisation was deemed to have occurred if the Scottish morbidity record contained an ICD9 or ICD10 code for any type of heart failure as the main condition pertaining to a hospitalisation episode. Where a diagnostic code for heart failure was included solely as “Other condition” the hospitalisation was deemed not primarily due to heart failure.

11.5 Results

11.5.1 Population

A total of 3815 pacemakers were implanted during the median study period of 4.96 ± 4.6 years.

820 (22%) patients (median age 73, range 22-103yrs, 57% males) were identified as having complete AV block as the reason for implant and were included in the analysis. During the study period there were 540 deaths. 278 (34%) patients had received RASBs. Overall median compliance with RASB therapy was 86 %.

There were a range of ACEI/ARB agents prescribed during the study; Ramipril (26%), Lisinopril (18%), Perindopril (16%), Valsartan (12%), Losartan (11%), Irbesartan (6%), Enalapril (5%), Candesartan (2%), Captopril (2%), Telmisartan (1%) and Quinapril (1%).

11.5.2 Comparison of patients with and without RASBs

The baseline characteristics of study patients with and without RASBs are detailed in Table 1 (below). Patients on RASBs had significantly more cardiovascular risk, with a higher prevalence of diabetes (24% vs. 9%, $p<0.001$), and prior myocardial infarction (18% vs. 5%, $p=0.03$). There was also a significant difference in prescriptions for aspirin, beta-blockers, calcium channel

blockers and statins between the groups at baseline. There was no significant difference in on-treatment mean arterial pressure between the two groups where this was available in 307 patients.

Table 11.1 – Baseline Characteristics

Characteristic	RASB	No RASB	P
No. of patients	278 (34 %)	542 (66%)	
Mean age at implant (yrs)	74.3 ± 10.3	72.8 ±20.4	0.234
Male	159 (70 %)	464 (62%)	0.007
Mean Deprivation score[$]	3.1	3.1	0.545
Diabetes	68 (24%)	49 (9%)	<0.001
Atrial Fibrillation	53 (19%)	51 (9%)	<0.001
Prior myocardial infarction	51 (18%)	28 (5 %)	<0.001
Left Ventricular Systolic dysfunction¬	83 (25%)	48 (10%)	<0.001
Mean Arterial Pressure (mmHg)[#~]	95 ± 9	97 ± 9	0.109
Mean Hb (g/dl)[#]	12.8 ± 1.5	12.8 ± 1.5	0.686
Mean Creatinine (mmol/L)[#]	116 ± 38	125 ± 58	0.02
Ventricular Systems	112 (40%)	277 (51%)	0.01
Dual Chamber Systems	166 (60%)	265(49%)	0.01
Aspirin	123 (44%)	123 (23%)	<0.001
Beta-blocker	115 (40%)	90 (17%)	<0.001
Dihydropyridine Calcium Antagonist	22 (7%)	26 (5%)	0.01
Non-Dihydropyridine Calcium	117 (42%)	91 (17%)	0.03
Statin	82 (29%)	71 (13%)	<0.001

 # Values are mean from date of implant to study end, $ Lower deprivation score is associated with higher lever of deprivation.~ Blood pressure only available for 307 individuals, (37% of cohort) , ¬LV systolic dysfunction defined as echocardiogram with LV EF < 40%.

11.5.3 Pacing mode

There was a significantly higher use of dual chamber systems in patients receiving

ACE/ARB agents (60% v 49%,p<0.001).

11.5.4 Effect of RASBs on outcomes

There were a total of 540 all-cause deaths in the entire study period. The cause of death was defined as cardiovascular in 44% of the RASB group and 55% of the non-RASB group (p<0.001).

Unadjusted and adjusted hazard ratios (HR) for all-cause mortality are shown in Table 2, and the full proportional hazards model is shown in table 3. RASB therapy was independently associated with a significantly reduced all-cause mortality (Figure 1) (adjusted HR 0.67; 95%CI [0.47 – 0.94], p<0.001 and a significant reduction in the incidence of heart failure hospitalisation after pacemaker insertion (adjusted HR 0.42 [95% CI 0.17-0.92) p< 0.001).

In a propensity score matched analysis of 389 individuals the HR for all-cause mortality was 0.57 [95%CI 0.39 – 0.67], p< 0.001; furthermore, when incorporating a time-dependent variable for ACEI/ARB use the result was also similar (HR 0.63 [95% CI 0.44 – 0.90] p< 0.001].

Figure 11.1 – Survival by RASB therapy

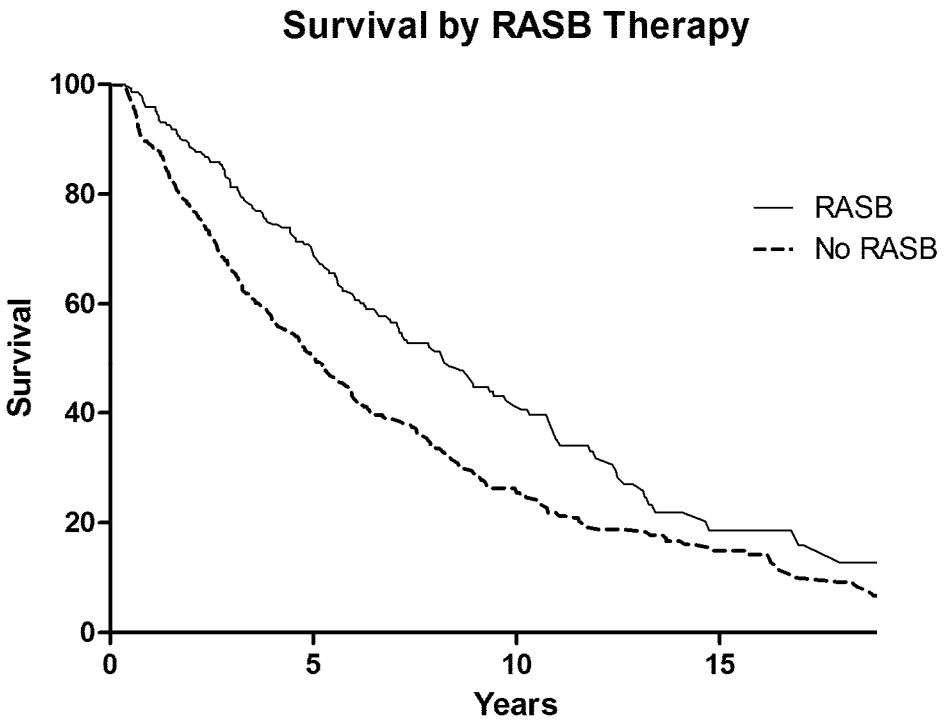


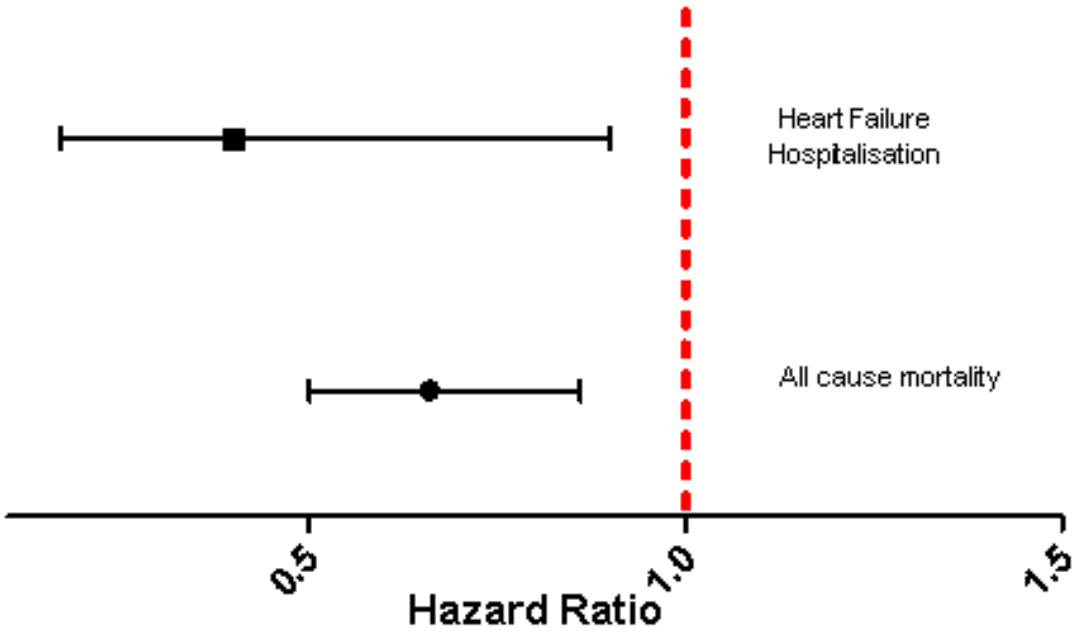
Table 11.2- Proportional Hazards model for risk of death

Variable	Hazard	P Value
ACE use (Y/N)	0.67 (0.47 – 0.94)	0.02
Age Paced (per year)	1.06 (1.04 – 1.07)	0.001
Male Sex	1.37 (1.08 – 1.74)	0.09
Diabetes (Y/N)	1.19 (0.87 – 1.65)	0.27
Aspirin use (Y/N)	1.01 (0.75 – 1.33)	0.97
Beta-blocker use (Y/N)	0.83 (0.61 – 1.14)	0.27
Loop Diuretic use (Y/N)	1.60 (1.2 – 2.1)	0.01
Statin use (Y/N)	1.56 (1.1 – 2.1)	0.01
Calcium Antagonist use (Y/N)	1.11 (0.82 – 1.51)	0.49
Left Ventricular dysfunction (Y/N)	1.42 (0.84 – 2.37)	0.19
Myocardial Infarction (Y/N)	1.36 (0.92 – 1.99)	0.11
Atrial Fibrillation (Y/N)	1.10 (0.79 – 1.51)	0.57
Haemoglobin (per 1g/dl)	0.89 (0.82 – 0.96)	0.04
Creatinine (per mg/dl)	1.01 (1.00 – 1.01)	0.03
Deprivation Score (quintile)		
1 (lowest)	Ref	
2	0.94 (0.65 -1.36)	0.74
3	0.83 (0.57-1.22)	0.35
4	0.71 (0.54-0.99)	0.04
5(highest)	0.76(0.54-1.09)	0.15
DDD vs VVI pacing	0.75 (0.58-0.96)	0.001

Table 11.3 – Outcomes according to RASB therapy.

	Unadjusted HR [95%CI]	Adjusted HR [95%CI]	Propensity Matched [95%CI]
All-cause mortality	0.57 [0.47 – 0.70] p<0.001	0.67 [0.47-0.94] p <0.001	0.57 [0.44-0.72] p=0.001
Heart Failure	0.53 [0.29 – 0.95], p<0.001	0.42 [0.17 – 0.92], p<0.001	-

Figure 11.2 – Adjusted Hazards for heart failure hospitalisation and all-cause mortality with RASB use.



11.5.5 Other factors determining survival

In our multivariate model (table 2), other factors independently associated with worse outcome included advanced age, higher social deprivation, loop diuretic and statin use and rising creatinine.

DDD pacing mode and higher serum haemoglobin were associated with improved survival.

11.6 Discussion

The effects of right ventricular pacing on cardiac function have been increasingly studied over recent years and with this has developed an understanding of potentially detrimental effects of right ventricular apical pacing. Right ventricular apical pacing is associated with dyssynchronous activation of the ventricles, neurohormonal activation and abnormalities of myocardial perfusion(188) in addition to acute and chronic worsening of cardiac output and endothelial function and this in terms may lead to adverse remodelling(59).

In this study I examined whether RASB therapy may offer beneficial effects in such patients. Indeed, RASB prescription was associated with a 58% relative risk reduction in heart failure hospitalisation (adjusted HR 0.42; 95% CI (0.17-0.92)) and a 33 % relative risk reduction (adjusted HR 0.67; 95%CI [0.47 – 0.94]) in all-

cause mortality.

The main counter argument to these findings is of course the potential association between RASB therapy and survival, however in this study, as might be expected, a significantly higher incidence of diabetes and coronary artery disease at baseline. Yet despite this, the study demonstrated survival and heart failure benefits associated with RASB prescription. Importantly there were no observed differences in blood pressure, where this was available, adding credence to the survival benefit not being due to blood pressure reduction. It should also be noted that no survival benefit was noted for aspirin, statin, or beta-adrenoceptor blocking therapy.

11.6.1 Why could RASB agents mitigate against pacing induced heart disease ?

Pacing induced heart disease has gained recognition but is as yet only partially understood. Whilst the mechanisms can be appreciated the mechanisms that underlie these are still being explored(141). RASB agents are known to reduce afterload and left ventricular wall stress and these key measures are known to be associated with ventricular dyssynchrony(117, 193). It might be expected therefore that RASB agents would offer benefits to these patients as they reduce left ventricular wall stress and limit adverse remodelling(111, 112), reduce myocardial fibrosis (113) and have also been shown to modulate sympathetic activity (114) which is also an important pathophysiological process in pacing induced heart disease (76). As previously described pacing

induced heart disease is associated with reduced systemic vascular resistance and afterload together with impaired endothelial function, once again measures that are known to be improved by RASB administration(115). Furthermore, no benefit was associated with use of calcium channel blockers in this cohort, suggesting that the benefit of RASBs was not through after load reduction alone, and that the adjuvant effects of neurohormonal interactions are likely to play a role.

It may be surprising therefore that the use of RASB in pacing induced dyssynchrony has not been formally studied until now. There have been animal studies in dog pacing models where RASB agents have been shown to reduce fibrosis and adverse left ventricular remodelling (116) and reduce left ventricular dyssynchrony during progression of heart failure (117). In that study, the total systemic resistance, arterial elastance, left ventricular end diastolic pressure and myocardial collagen density were significantly lower in the ACEI treated group of dogs compared to controls.

There has been some study of the benefits of RASB agents in humans with pacemakers. RASB had a trend to reduction in atrial fibrillation in a study of subjects with dual chamber pacemakers by Williams et al (118). It is therefore plausible that the benefits of RASB were due to a reduction of atrial fibrillation, as this was not recorded per se. It should be noted that any correlation between the two remains speculative(194). Even with this potential association the study shows a benefit to prescription of RASB in this group and the mechanisms warrant further study.

It should also be considered that RASB agents have been shown to offer general cardio-protective effects and large landmark studies such as HOPE(195), SOLVD(196) , SAVE(193) and ONTARGET(197) have all shown benefits of RASB use in at risk populations.

Without a full understanding of the mechanisms, which is beyond the scope of this retrospective cohort study, one can only hypothesise how RASB agents may offer benefits in paced patients and this should be the focus of further study.

11.7 Limitations

The limitations of the study are those inherent with any retrospective, non-randomized, observational study. However, the current study reflects the true population and a “real world scenario” in a large cohort. In common with all observational studies, it was impossible in this study to account for all confounding influences that may have biased the observed differences between the groups considered. In this respect, those in the RASB group had a higher incidence of significant comorbidities including atrial fibrillation, diabetes and prior myocardial infarction at baseline which may explain why these patients were originally prescribed these drugs. Additionally, more patients in the RASB group were prescribed beta-blockers in keeping with the higher incidence of ischaemic heart disease with prior myocardial infarction. Arguably, these differences at baseline, if anything, would suggest that those in

the RASB group were actually at a much higher risk compared to patients who did not receive such therapy. Despite this higher risk at baseline, we found that patients with pacemakers who received ACEI/ARB therapy had a significantly better outcome. In addition, the RASB group received relatively more dual chamber pacemakers than single chamber ventricular (VVI) Pacemakers (60% versus 49%). This was not explained by prevalence of atrial fibrillation (AF) as more patients in the treated group had underlying AF (19% versus 9%). Although his difference in pacing mode may plausibly account for the differences we observed, the large RCTs (UKPACE(191) and CTOPP(37)) did not show benefit of dual chambered pacing against VVI pacing on heart failure outcomes and survival, in patients with AV nodal disease, therefore our results are not likely to be due to differences in the pacing mode between the two groups. Another limitation was that the individual intensity of RASB exposure was not measurable because of multiple formulations and changing doses. However, to minimise potential treatment bias and baseline imbalance of co-variants between the groups, we also performed a propensity score matched analysis. This propensity score matched analysis has been shown to eliminate up to 90% of treatment bias in observational studies(198, 199).However, only a randomized controlled trial can truly remove bias and reliably measure exposure to treatment. Nevertheless, we believe that this study reliably captured the presence of RASBs and reflects prescribing in clinical practice. Blood Pressure data were only available for a limited number of subjects in the study. Whilst it is possible that the effects seen in this study may have occurred due to blood pressure reduction, we identified no difference in blood pressure

between the two groups where this was available.

Although we do not have the percentage pacing for the non survivors due to the lack of records of deceased patients, we limited our study cohort to those with a high degree of ventricular pacing by identifying patients with non-reversible complete AV block as the underlying pacing indication.

11.8 Conclusions

Measures to avoid pacing induced cardiovascular disease have, to date, focused on development of pacemaker algorithms to avoid unnecessary right ventricular pacing and alternative pacing sites. However, 40% of pacemaker patients have atrio-ventricular node disease and require long term pacing in the ventricle 18. Furthermore, alternative pacing sites may not be applicable or feasible in all these patients. This study suggests that RAS blockade may offer a pharmacological strategy to ameliorate some of the deleterious effects of chronic right ventricular apical pacing. Although this is an observational study, the results are hypothesis generating and the data support the case for a prospective randomized placebo controlled trial of RASB in patients likely to be exposed to high frequency of RV pacing.

12. Conclusion

This series of studies have illustrated:

- A significant proportion of patients referred for conventional pacemaker insertion have impaired left ventricular systolic function.

- High degrees of right ventricular apical pacing is associated with acute impairment of endothelial function.

- Biventricular pacemaker implantation in patients with impaired systolic function results in increase exercise tolerance, reduced markers of inflammation, less impairment of endothelial function and improved quality of life.

- Patients with complete heart block who are receiving renin angiotensin modifying agents have reduced mortality and reduced incidence of heart failure hospitalisation.

Patients with impaired left ventricular systolic function are at risk of pacing induced heart disease and should be considered for biventricular pacemaker insertion.

13. Future Study

It remains unclear why some patients exposed to right ventricular pacing for long periods are unaffected by some of the deleterious effects described. Further work needs done to determine whether there are markers that may signal which patients are most at risk of pacing induced heart disease and who may derive the most benefit from biventricular pacing systems. Additionally whilst the old adage of prevention is better than cure holds true, work needs to explore both avenues.

Prevention

Major studies discussed in this thesis have shown that biventricular pacemaker insertion for patients with left ventricular systolic dysfunction who require ventricular pacing is beneficial and may ameliorate the effects of right ventricular apical activation. A newly proposed “leadless” pacing system of the future could potentially permit pacing at any point within the heart and thus as skill and technology develop targeting pacing of the his bundle or even direct to the purkinje fibres may be feasible and offer further avenues for study.

Cure

Perhaps better entitled amelioration I have discussed the potential for pharmacology amelioration of the effects of right ventricular apical pacing and further study should include a prospective randomised trial to validate these findings. This should be undertaken in two phases with a smaller pilot study allowing data to be collected on the measures of cardiovascular health on those taking RASB agents or placebo, and then a subsequent larger study to

determine whether there is an outcome benefit in terms of a reduction in heart failure hospitalisation or all-cause mortality.

The two interventional studies described in this thesis both sought to measure the potential effects of different pacing parameters and sites on endothelial function. These studies both measured endothelial function non-invasively using the EndoPAT technology. Further work is needed in an attempt to determine the mechanism behind the improved RH-PAT index and this would be best explored by studying patients with biventricular pacemakers in situ and studying varying different measures of endothelial function and endothelial health during RV and Biventricular pacing arms.

One of the hypotheses for some of the effects on the endothelium is the alteration to laminar flow. MRI has conventionally been the modality of choice to assess vascular flow patterns and until recently pacemakers in situ have been a contra-indication to MRI scanning. With the advent of the MRI safe pacemaker it would now be possible to conduct further study to assess changes in aortic, coronary and peripheral wall stress and assess changing flow patterns.

14. Appendices

14.1 Patient Information Sheet (Right Ventricular Pacing and its effects on endothelial function in man.)

UNIVERSITY OF DUNDEE

Division of Medicine and Therapeutics

Professor of Cardiology
Professor Chim C Lang BMSc MD FRCP FRCPE FACC

Patient information Sheet

Endothelial Function and Cardiac Output during and after right Ventricular Pacing

We invite you to participate in a research project. We believe it to be of potential importance. However, before you decide whether or not you wish to participate, we need to be sure that you understand firstly why we are doing it and secondly what is involved if you agree. We are therefore providing you with the following information. Read it carefully and be sure to ask any questions you have. And, if you want, discuss it with outsiders. We will do our best to explain and to provide any further information you may ask for now or later. You do not have to make an immediate decision.

Investigator
Professor Chim C Lang MD FRCP, Division of Medicine and Therapeutics, Division of Cardiology, Ninewells Hospital and Medical School, Tel: 01382-496374, C.C.Lang@dundee.ac.uk

Why is this study being done?
You have been given a dual chamber pacemaker for a slow heart rate. This type of pacemaker can be switched on in the upper heart chamber (the right atria) and the lower heart chamber (the right ventricle). There is increasing evidence that pacing in the right ventricle may in the long term (usually over many years) be deleterious and may result in an increased risk of stroke, and heart failure. The purpose of this study is to help understand the mechanism how and why right ventricular pacing may be deleterious, and thus lead to better pacing sites and technology.

What this study entails
You will be required to visit the pacemaker clinic area for 6 visits over 5-6 weeks (see Supplementary information Sheet) and your pacemaker will be programmed to different modes and rates of pacing, lasting at least a week each. During the study, there is no risk of your heart rate falling to less than 55 beats per minute

At the beginning and end of each different pacing mode, two tests will be carried out. These tests are non-invasive and will assess the efficiency of your heart (cardiac output) and the function of your blood vessels (endothelial function). A blood sample will also be collected at these visits. The amount of blood taken will be 10mls i.e.2 teaspoonfuls. This blood sample will be stored and tested in the laboratory in Department of Clinical Pharmacology, Ninewells Hospital.

1. Cardiac output measurements will be done at rest and on exercise and will involve you walking on a tread-mill for about 20 minutes, whilst breathing through a mouth piece. You will be attached to an ECG machine during the procedure, to record you heart beat.
2. The endothelial function test will involve inflating a blood pressure cuff around both your arms for about 3 minutes, and a clip on a finger to record blood flow.

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You will be reimbursed for your transport for each visit (based on receipts and tickets where appropriate) or we will arrange transport for you, whichever is more convenient for you.

Will I have my pacing mode and rate changed to that used in this study after it finishes?

At the end of the study, your pacemaker will be programmed to your pre-study setting. However, if during the study we identify a pacing mode that is unfavourable to you in terms of your cardiac function, this information will be conveyed to cardiologist and general practioner. Decisions to change your programming will be taken by your cardiologist, after taking all factors into consideration.

What are the risks, discomforts of the study?

If you have critical coronary artery disease that has not been previously diagnosed, overdrive pacing and treadmill exercise may cause angina.
During measurement of endothelial dysfunction, inflation of the blood pressure cuff may cause temporary localised discomfort.
Exercise cardiac output measurements may cause exhaustion, but you will be asked to do only what is within your capacity.

Can I withdraw from the study?

You can withdraw from the study at any time, and you are not obliged to give a reason, but you will need to have your pacemaker programmed to the original setting. Your further management at the pacemaker clinic will not be affected in any way.

What will become of the Information?

The information will be stored securely in the Department of Clinical Pharmacology, Ninewels Hospital. Access to the information will be available to the researchers and yourG.P. only.You will be able to receive your details from either Professor C.C. Lang or your G.P.The overall findings from the study may be published in reputable medical journals.No individual patient will be identifiable.

What are my rights?

You can obtain more information from Prof.C.C.Lang. You can take as long as you like to decide and you can change your mind at any time and withdraw from the study without it affecting your normal treatment.

Participation in this study is entirely voluntary, and you are free to refuse to take part or withdraw at any time without giving a reason and without this affecting your future medical care or your relationship with the medical staff looking after you.

The Tayside Committee on Medical Research Ethics, which has responsibility for scrutinising all proposals for medical research on humans in Tayside, has examined the proposal and has raised no objections from the point of view of medical ethics. It is a requirement that your records in this research, together with any relevant medical records, be made available for scrutiny by monitors from NHS Tayside.

Thank you for considering taking part in our study.

Contact Person

Professor Chim C Lang
Division of Medicine and Therapeutics
Ninewells Hospital and Medical School
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Patient Information Sheet (Choice Study)

Participant Information Sheet (PIS)

THE CHOICE Trial: CHoosing the RIght PaCing Mode in Heart FailurE : *Should heart failure patients with bradycardia receive biventricular pacemakers rather than conventional pacemakers?*

We would like to invite you to participate in a research project. We believe it to be of potential importance. However, before you decide whether or not you wish to participate, we need to be sure that you understand firstly why we are doing it and secondly what is involved. We are therefore providing you with the following information. Please read it carefully and be sure to ask any questions you have, and if you wish, discuss it with your family members or your GP. We will do our best to explain and to provide any further information you may ask for now or later. You do not have to make an immediate decision.

Investigators

Dr Douglas H J Elder, Department of Cardiology, Ninewells Hospital, Ninewells Hospital and Medical School, Tel: 01382-632330, delder@nhs.net

Dr Anna Maria Choy, Division of Cardiology, Division of Medicine and Therapeutics, Ninewells Hospital and Medical School, Tel: 01382-632330, A.Choy@dundee.ac.uk

Why is this study being done?

You are to be given a pacemaker for a slow heart rate and a scan of your heart (Echocardiogram) shows that your heart pumping ability is reduced compared to normal. Conventional pacemakers used to treat slow heart rates are

traditionally placed in the right side of the heart. Recently, new pacemakers (biventricular pacemakers) have been developed which stimulate (pace) your heart from both sides (left and right) at the same time and have been previously shown to be safe and effective in improving symptoms in people with poor heart function. We are investigating whether implanting one of the new biventricular pacemakers into people such as you will be better compared to a conventional pacemaker.

What this study entails

You will be given a pacemaker that paces both sides of the heart (biventricular pacemaker), rather than a conventional pacemaker that paces only the right side. This means that your pacemaker operation will be longer that usual.
You will be required to visit the clinical pharmacology department for 5 visits over the course of a year (see Supplementary information Sheet) and your pacemaker will be programmed to different methods of pacing for 6 months at a time.

At each visit you will undergo a series of tests. These tests are non-invasive and will assess the efficiency of your heart (cardiac output), the function of your blood vessels (endothelial function) and how far you can walk in 6 minutes. (6 minute hall walk test). A blood sample will also be collected at these visits. The amount of blood taken will be 20mls i.e.2 tablespoonfuls. This blood sample will be stored and tested in the laboratory in Department of Clinical

Pharmacology, Ninewells Hospital. The sample will be stored until completion of the study.

1. Cardiac output measurements will be done at rest and cycling on a stationary bicycle, to a level within your limits whilst breathing through a mouth piece. You will be attached to an ECG machine during the procedure, to record you heart beat.
2. The endothelial function test will involve inflating a blood pressure cuff around both your arms for about 3 minutes, and a clip on a finger to record blood flow.
3. 6 Minute walk test will involve walking at your usual pace continuously for 6 minutes. You may stop and rest at anytime prior to continuing. The distance you have walked will be recorded.

You will be reimbursed for your transport for each visit (based on receipts and tickets where appropriate) or we will arrange transport for you, whichever is more convenient for you.

Will I have my pacing mode and rate changed to that used in this study after it finishes?

At the end of the study, your pacemaker will be programmed to which ever setting was best for you.

What are the risks, discomforts of the study?

By entering this study you are agreeing to have a biventricular pacemaker inserted, instead of a conventional pacemaker. A biventricular pacemaker provides 3 pacing leads into the heart, compared with 2 required for a

conventional pacemaker. The third lead will be positioned in one of the veins around the heart called the coronary sinus, or in the middle wall of the heart if the vein is anatomically not suitable. Insertion of this third lead if often technically more difficult than the two conventional leads.

Therisks of the pacemaker insertion procedure in particular a collapsed lung are increased by 1%. There will also be additional X-ray screening to place the third lead, and this is estimated to be 30 minutes in total. This is about the same as you would be exposed to in 10 years of normal life or about the same as having a CT scan of your torso.

Some patients, despite initial good placement of the leads, have problems with a lead not working properly. This may result in a sensation of regular hiccups. This is not dangerous and can be stopped by changing the programming of the device. The specific risk associated with implantation of the additional third lead include damage to the coronary sinus vein (1%), There is a very small risk of worsening kidney function if special X-Ray contrast is used.

During measurement of endothelial dysfunction, inflation of the blood pressure cuff may cause temporary localised discomfort. Taking of 20mls (2 tablespoons) of blood from the vein in your arm at each visit may be associated with some mild localised discomfort. Exercise cardiac output measurements may cause tiredness, but you will be asked to do only what is within your capacity.

You will be asked to complete two written questionnaires. These take approximately 5 minutes each.

Can I withdraw from the study?

Participation in this study is entirely voluntary, and you are free to refuse to take part or withdraw at any time without giving a reason and without this affecting your future medical care or your relationship with the medical staff looking after you.

You will need to have your pacemaker programmed to the original setting.

What will become of the Information?

The information will be stored securely in the Department of Clinical Pharmacology, Ninewells Hospital for 15 years after the completion of the study. Access to the information will be available to the researchers and your GP only. You will be able to receive your study results from either Professor C.C. Lang or your GP .The overall findings from the study may be published in reputable medical journals and will provide valuable information in determining what type of pacemaker is best for patients like you. No individual patient will be identifiable.

What are my rights?

You can obtain more information from Dr D Elder or Dr Choy. You can take as long as you like to decide and you can change your mind at any time and withdraw from the study without it affecting your normal treatment.

The Tayside Committee on Medical Research Ethics, which has responsibility for scrutinising all proposals for medical research on humans in Tayside, has examined the proposal and has raised no objections from the point of view of medical ethics. It is a requirement that your records in this research, together with any relevant medical records, be made available for scrutiny by monitors from NHS Tayside.

Thank you for considering taking part in our study.

Contact Person

Dr. Douglas H J Elder

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Ninewells Hospital and Medical School

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Complaints

If you believe that you have been harmed in any way by taking part in this study, you have the right to pursue a complaint and seek any resulting compensation through the University of Dundee who are acting as the research sponsor. Details about this are available from the research team. Also, as a patient of the NHS, you have the right to pursue a complaint through the usual NHS process. To do so, you can submit a written

complaint to the Patient Liaison Manager, Complaints Office, Ninewells Hospital (Freephone 0800 027 5507). Note that the NHS has no legal liability for non-negligent harm. However, if you are harmed and this is due to someone's negligence, you may have grounds for a legal action against NHS Tayside but you may have to pay your legal costs.

14.2 Medical Physics Dose Assessment

Dose summary for Choice Trial

It is reported in the literature [1] that the proposed BiVentricular device insertion will increase screening time and patient dose by a factor of 4 compared with conventional pacemaker insertion. This results in a screening time of 22 mins compared with conventional pacemaker insertions undertaken in the Bronchoscopy suite Ninewells Hospital. The effective dose to patients undergoing BiVentricular pacemaker insertion with a screening time of 22 minutes has been estimated at 15mSv. At 35 mins screening time, the mean screening time reported in [1], the effective dose increases to 24mSv. This is considered a high dose procedure and is comparable with CT of the Chest Abdomen and Pelvis. The risk of radiation induced fatal cancer induction for the adult population from 24mSv effective dose is 5% per Sv or 1 in 800, which is considered to be a moderate risk.

It is our recommendation that the fluoroscopy frame rate must not exceed 12.5 frames per second during this procedure as the equipment is capable of doubling the patient dose.

Peak skin entrance dose rates must be kept below the deterministic level of 2Gy by maintaining fluoroscopy at or below 12.5fps. Where the procedure exceeds 35 mins in screening time, the frame rate should be reduced below 12.5fps .The High Quality high dose mode for cine recording should be avoided.

All estimates of patient dose are based on the Ziehm Vision R fluoroscopy equipment in use in the Bronchoscopy suite, operating at a maximum fluoroscopy frame rate of 12.5 frames per second.

[1] Fluoroscopy Guided Implantation of Modern Cardiac Resynchronization Devices. Radiation Burden to the Patient and Associated Risks . K Perisinakis, N Theocharopoulos, J Damilakis, E Manios, P Vardas, and N Gourtsoyiannis. Journal of American College of Cardiology, Vol 46, No.12, 2005

24th July 2009

Janice O'Neill
Principal Physicist
Radiation Physics
Ninewells Hospital Dundee

14.3 Minnesota Living with heart failure Questionnaire

MINNESOTA LIVING WITH HEART FAILURE® QUESTIONNAIRE

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -	**No**	**Very Little**				**Very Much**
1. causing swelling in your ankles or legs?	0	1	2	3	4	5
2. making you sit or lie down to rest during the day?	0	1	2	3	4	5
3. making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4. making your working around the house or yard difficult?	0	1	2	3	4	5
5. making your going places away from home difficult?	0	1	2	3	4	5
6. making your sleeping well at night difficult?	0	1	2	3	4	5
7. making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8. making your working to earn a living difficult?	0	1	2	3	4	5
9. making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the foods you like?	0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5
13. making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14. making you stay in a hospital?	0	1	2	3	4	5
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side effects from treatments?	0	1	2	3	4	5
17. making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18. making you feel a loss of self-control in your life?	0	1	2	3	4	5
19. making you worry?	0	1	2	3	4	5
20. making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21. making you feel depressed?	0	1	2	3	4	5

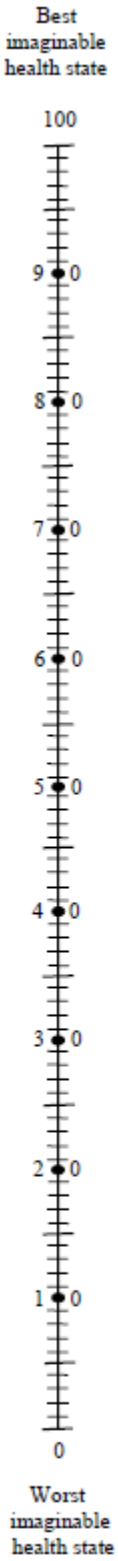
11/10/04

14.4 EuroQol Questionaire (VAS)

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



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